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OBSERVATIONS ON THE EXTENSOR PLANTAR REFLEX AND ITS RELATIONSHIP TO THE FUNCTIONS OF THE PYRAMIDAL TRACT

With Special Reference to (1) the Plantar Reflex in Infancy, (2) the Crossed Extensor Plantar Reflex and (3) Extension of the Great Toe as an Associated Movement

BY

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INTRODUCTION

THE physiological nature of the extensor plantar reflex has recently been the subject of considerable debate (Lassek, 1954; Marshall, 1954; Hoff and Breckenridge, 1956; Nathan and Smith, 1956; Walshe, 1956). We can conveniently summarize what we regard as the established state of our knowledge with regard to this reflex by quoting from the conclusions of the paper by Walshe (1956). "The present writer in 1914 attempted an analysis of the flexion-reflex in man and came to the conclusion that the Babinski plantar response was an integral part of this, and was sometimes associated with an accessory crossed extension reflex of which the striking component was the crossed plantar (plantar flexor) response. A comparative analysis of this reflex in man and the nociceptive flexion-reflex described by Sherrington (1910) was also made, and the conclusion expressed that the two phenomena were strictly homologous. The validity of this view has recently received additional confirmation from Kugelberg's electromyographic analysis of the A and C fibres in this response in man." Walshe in his paper critically considers the views of those who hold that a correlation between the extensor plantar reflex and impaired function of the pyramidal tract has not been established, and reaffirms his own view as follows: "It may well be that the pyramidal system has not yielded up all the secrets of its constitution, origin and activities, and that at some future time research may reveal within what we now call the pyramidal system separable elements, to the state of activity of one of which it may be possible to relate the Babinski response. At present, however, 'busy common sense' which has been too long absent from this particular scene,

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requires us to look upon the Babinski response as standing in relation to the pyramidal system." The extensor plantar reflex, therefore, is to be regarded as part of the flexion reflex of the lower limb; this is considered to be homologous with the flexor withdrawal response to a nocuous stimulus described by Sherrington, and as a manifestation of impaired function of the pyramidal tract. We use the term "impaired function" rather than degeneration, for, as Walshe points out, Babinski's sign may appear transiently in temporary states of disorder of cerebral function due to what we now speak of as biochemical lesions. However it was hardly to be expected that the statement, now nearly half a century old, that the extensor plantar response is part of a nociceptive reflex, would prove to be the last word on the subject, since it raises further questions which call for further clinical observations. Sherrington (1910) discussing the nociceptive flexion reflex in animals, states that "this reflex is elicitable from all points of a large area of the limb surface and also though less easily from the deep structures as well." Walshe (1914–15), writing of this receptive field of the flexion reflex in man, states that "when the reflex is well developed, cutaneous stimuli applied to any part of the limb surface, and even to the lower part of the abdominal wall, will elicit a reflex complete in form. However, as we recede from the free extremity of the limb, the threshold of stimulation rises, and stronger and more prolonged stimuli are needed to evoke any response." The sole, therefore is "the most essential part of the receptive field." Riddoch (1917) also noted that the reflexogenous area for the flexion reflex of the lower extremity extends from the sole to the abdominal wall. From any part of this field the typical reflex can be elicited, but in that evoked from the abdominal wall and the groin flexion at the hip and knee and adduction of the thigh are the prominent movements, and the feet and toes may be affected slightly, or even not at all. On the other hand dorsiflexion of the foot and upgoing toes are outstanding features of the reflex effect when the sole is the part stimulated. Since then it has been widely recognized that after a severe lesion of the spinal cord in the lower cervical or upper dorsal region the flexion reflex of the lower limb may sometimes be elicited by an appropriate stimulus, e.g. pin-prick, applied to the upper part of the chest wall. In one of our patients, described in this paper, it could even be elicited by pin-prick applied to the face. Fulton and Keller (1931) have noted that in the baboon the reflexogenous zone of the flexion reflex actually spreads throughout the entire body. Hence the interpretation of the extensor plantar reflex as part of the flexor withdrawal response of the lower limb to a nocuous stimulus is physiologically inadequate until it can explain why a reflex which would be biologically the appropriate response to a scratch on the sole is in some cases elicitable by a prick on the upper part of the chest, or even the head.

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The occurrence of the extensor plantar reflex in the normal human infant has plausibly been attributed to the absence of myelination of the pyramidal tracts in infancy, yet some caution is necessary before equating a sign produced by disease in man and experimental lesions in animals with a normal state of affairs in infancy. Though the normal infant manifestly lacks the movements mediated by the pyramidal tracts, it does not exhibit the disorders of muscle tone and tendon reflexes associated with pyramidal lesions. Any complete account of the physiology of the extensor plantar reflex in man must include a description of the physiological factors which influence it in infancy. It occurred to us that light might be thrown upon the receptive field for this reflex after lesions of the nervous system by studying the extent of that field, and the response to different types of stimulus, in children from immediately after birth onwards. We discuss these observations in relation to previous studies of the reflex activity of animal and human fœtuses, and the human infant, and to what is known about myelination in the nervous system at the relevant ages. In congenital diplegia it is generally agreed that, whatever other ganglion cells and tracts may be involved, the pyramidal tracts remain in a state of incomplete development. We have therefore studied a series of children with congenital diplegia, applied the same tests to them, and compared their responses with those of normal infants. Since the receptive field of the flexion reflex of the lower limbs sometimes extends to the chest when there is a lesion of the spinal cord in the cervical or upper thoracic region we applied our series of tests also to five adult males with long-standing—virtually complete—traumatic lesions of the cervical cord between the fourth and sixth segments.

Collier (1899) appears to have been the first person to observe the behaviour of the opposite foot when the plantar reflex is elicited. He noted that plantar flexion of the opposite great toe is the usual response, whether the reflex on the side stimulated is flexor or extensor. He reported, however, that he had met with two cases of slight extension of the toes as a "crossed plantar reflex" in severe spastic paraplegia.

Walshe (1914–15) and Riddoch (1917) later drew attention to the fact that in paraplegia in man the extensor plantar reflex in one lower limb is commonly associated with an increase in the extensor tone, and plantar flexion of the great toe, in the opposite lower limb, a reaction homologous with the crossed extension reflex in animals. Walshe also noted that occasionally in paraplegia the response to a scratch on the sole was not only an extensor plantar response on the side stimulated, but also an upgoing toe on the opposite side. "In the extended form of spastic paralysis of the lower limb," he wrote, "homolateral flexion is always accompanied by crossed extension, when any crossed reflex is seen, and this connotes crossed plantar flexion of foot and toes. However, where

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the reflex activity of the extensors is relatively less than that of the flexors—namely in paraplegia-in-flexion, and in conditions transitional between this and the extended form of spastic paralysis—we do see a crossed flexion reflex with its integral 'extensor response.' In such cases occur bilateral spontaneous flexor spasms. Sherrington has noted, in certain parallel circumstances, the occurrence of crossed reflex flexion. In man, therefore, as in animals, there is this occasional exception to a general rule laid down by Sherrington, that in the hind-limbs of the spinal animal simultaneous reflex movements are opposite in phase in the two limbs."

Riddoch (1917), describing the reflex functions after complete division of the spinal cord in man, observed that in 2 out of 8 cases stimulation which induced a flexion reflex of one lower limb caused an associated contraction of the extensor muscles of the other one. But he said that by far the most common crossed response was flexion, most at hip and knee, associated with adduction of the thigh. He does not specifically mention the behaviour of the toes of the opposite foot.

In the routine examination of patients suffering from organic nervous disease we have observed in a small proportion of cases that scratching the sole of one foot would evoke extension of the great toe of the opposite one, and sometimes this has even occurred when direct stimulation has produced a flexor response. This, therefore, has been an exception to the much commoner observation, noted by Walshe and Riddoch, that when stimulation of one sole evokes an extensor plantar reflex the common associated reflex movement on the opposite side is one of extension of the limb with plantar flexion of the great toe. It has not been our experience that this crossed extensor plantar reflex has occurred only in association with severe lesions of the spinal cord leading to flexor spasms, as noted by Walshe. The second part of this paper is devoted to a record of our observations on, and a discussion of the clinical significance of, the crossed extensor plantar reflex.

Our attention having been directed to the movements of the great toe in various circumstances, we noted also that it normally becomes dorsiflexed in association with dorsiflexion of the foot against resistance. When a patient is asked to flex the hip and knee against resistance, however, different forms of this associated movement occur. We have therefore investigated it in both normal subjects and in patients with a pyramidal lesion.

We end this paper with a discussion of the physiological nature of the extensor plantar reflex in the light of these new observations, and their significance in relation to the functions of the pyramidal tract.

The Flexion Reflex in the Human Infant

Langworthy (1935) has reviewed previous studies of the reflex behaviour of fœtal and infant mammals and endeavoured to correlate this with the

myelination of the nervous system. In even the youngest fœtal kitten studied, in which the total amount of activity is small, pinching a foot-pad causes an active withdrawal of the leg. On stimulation of one foot-pad flexion of that leg occurs and the opposite leg is extended. Minkowski (1920, 1921, 1926, 1927), studying the human fœtus, concluded that in the fœtus of three or four months the plantar reflex is a purely spinal phenomenon and results sometimes in extension and sometimes in flexion of the great toe. At the age of from 4 to 6 months a tegmental influence is superimposed upon this spinal mechanism and influences the relationship between the two antagonistic forms of reflex in favour of the extensor variety. This is shown by the fact that in such fœtuses transection between the upper extremity of the lumbar region of the spinal cord and the lower end of the mid-brain can lead to a reversal of the extensor plantar response, that is the fœtal Babinski reflex, into the flexor form. According to Minkowski this influence of the brain-stem upon the spinal reflexes is mediated by reticulospinal and tegmentospinal fibres descending in the anterior column of the spinal cord. The myelination of these tracts begins in the fourth month of fœtal life and in the sixth month is already well advanced. Later-developing factors which come to influence the plantar reflexes in the later part of fœtal life include the development of the striatum, the red nucleus, and the cerebellum. For the first few weeks after birth Minkowski has found that, contrary to the general opinion that the extensor plantar is the characteristic form of response, a flexor response is almost equally common.

Waggoner and Ferguson (1930) made detailed studies of the plantar reflex in infants from birth onwards, using two grades of stimuli. Throughout, the lighter stimulus tended to favour the extensor response, the heavier the flexor. Like Minkowski they obtained flexor responses from a substantial minority during the first week of life. From the tenth day onwards these were replaced by extension of all the toes or extension of the great toe with flexion of the others. By the sixth month 28 per cent gave a flexor reaction with the lighter stimulus and 99 per cent with the heavier. At one year the corresponding figures were 88 and 96 per cent. Waggoner and Ferguson suggest that during the first six months the plantar reflex is purely spinal. At that age thalamo-pallidal control develops without any corticospinal influence. At the age of 1 year corticospinal control has developed.

Schlesinger (1927) found that a flexor response persisted until the second month of life, being replaced by extension till the sixth month. He also stresses the influence of extrapyramidal systems prior to the development of the corticospinal tracts and like some other writers (Vogt and Vogt, 1908; Zador, 1927) believes that the extensor plantar reflex of early infancy exhibits distinctive features.

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Langworthy notes that the newborn child reacts to changes in temperature, but less strongly to temperatures warmer than the body than to those cooler, and states that the heat and cold pathways are myelinated to the level of the thalamus at birth. Keene and Hewer (1931) state that all important sensory pathways are myelinated by the 28th week of fœtal life, by which time the child is viable. Langworthy says that "the myelination of fibres in the cord does not begin until about the 5th month of fœtal life and is not complete until between the 15th and 20th years. It first becomes apparent in the anterior or posterior roots and the ventral commissure. Very soon afterwards the ventrolateral ground bundles begin to show scattered myelinated fibres and likewise a portion of the posterior funiculi. The corticospinal tract becomes myelinated between the ninth month and the second year. Although the anterior roots show the beginning of myelinization only slightly in advance of the posterior, the process is simpler in the anterior roots and their medullation is completed when not more than half the fibres of the posterior roots show any myelin." It is generally agreed that myelination tends to proceed distally from the cell body. Keene and Hewer note that there are four periods between the 12th week of gestation and one year after birth when myelination appears to receive an impetus (1) at about the 14th week of gestation, (2) from the 22nd to the 24th week, (3) just before full term and (4) about 8 months after birth.

Personal observations.—Our own observations on the plantar reflex in infancy are based on a study of 35 normal children ranging in age from 1 day to 27 months. They are set out in Table I. Our aim was to investigate the extent of the receptive field and the type of response obtained in relation to age and the kind of stimulus used. The sites selected for stimulation were the neck, the upper part of the chest at approximately the level of the third thoracic dermatome, the middle of the abdomen at the level of the tenth thoracic dermatome, the anterior and inner aspect of the thigh, and the outer aspect of the sole. Light touch, having been shown by experience to be on the whole ineffective as a stimulus, was discarded. At all levels mentioned pin-prick and cold were used as stimuli, first on one side and then on the other, the response of both the ipsilateral and the contralateral plantar reflex being noted. On the sole key-drag was also used. About half the observations were made on children between the age of 1 day and 6 months and the other half on children between the age of 6 months and 27 months.

It will be seen from Table I that:

(1) In children up to the age of 8 days the plantar responses obtained were almost always extensor. They could often be elicited by pin-prick or cold as high as the third thoracic segment, but at all levels,

including the sole, the response was often limited to the side stimulated, in contrast to children aged from 5 to 20 weeks.

(2) The children aged between 5 and 20 weeks showed the greatest activity of the extensor plantar reflex. The extensor plantar during this period occurred as a bilateral response to all of the three forms of stimulus applied to the sole. It could also be obtained bilaterally as a result of stimulating either thigh. A bilateral response could usually be obtained from the abdomen and from the upper chest, but the response was definitely or doubtfully flexor almost as often as it was extensor when elicited from these levels.

(3) After 21 weeks the receptive field shrinks progressively from above downwards. Save for one partial exception no child over the age of 23 weeks gave any plantar response to a stimulus at the third thoracic level, nor after 9½ months to one at the tenth thoracic level. After that age also stimulation of the thigh usually failed to elicit any response. From 20 weeks onwards the response to stimulation of the sole began to change. The extensor response became less definite, or was replaced by a doubtful flexor or even a frank flexor, and after the age of 8 months tended to be limited to the side stimulated, or to evoke only a weak response on the opposite side.

(4) With one or two exceptions cold ceased to be effective as a stimulus at the age of 24 weeks. In no case of a child over that age was it effective at the third thoracic level and in only one on the abdomen. On the neck cold appeared to be more effective than pin-prick, and in 5 cases elicited a bilateral extensor plantar response in children between the ages of 11 and 21 weeks.

(5) Even during the second year of life the response to a scratch on the sole was not by any means uniformly a definite flexor. Sometimes it was a weak flexor, sometimes a weak extensor and sometimes even a definite extensor.

It is tempting to try to correlate the behaviour of the plantar reflex in infancy with the myelination of the nervous system. The limitations of any such interpretation, however, are obvious. Even if we knew more than we do about the progress of myelination in the various tracts of the spinal cord, and if we assume that myelination is necessary for functional activity, the function of a particular efferent pathway is dependent not only upon its own ability to conduct nervous impulses, but also upon the capacity of afferent pathways to respond to stimuli, and the integration of sensorimotor responses at higher levels. Nevertheless, it is perhaps justifiable to draw certain limited conclusions from our observations.

(1) Since there is independent evidence correlating the extensor plantar reflex with impaired function of the pyramidal tract it seems likely that the conversion of the infantile extensor plantar reflex into the flexor

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response between the 9th and 24th month of life can be correlated with the progressive myelination of the pyramidal tract, which is known to reach completion during this period. Nevertheless in infancy, as in pathological states developing later in life, the extensor plantar response is part of the flexor reflex of the lower limb and in neither case can this be fully explained merely as a result of incomplete development or impaired function of the pyramidal tract, a point to which we return in the last section of this paper.

(2) It seems likely that the progressive shrinkage of the receptive field of the reflex from above downwards is also the result of the centripetal myelination of the pyramidal tracts, and there is independent evidence in support of this view. Zülch (1951) points out that the development of voluntary movement in the human infant begins in the 2nd to 3rd week with the eye movements and spreads caudally concurrently with the myelination of the pyramidal tracts as shown in his diagram, fig. 1,

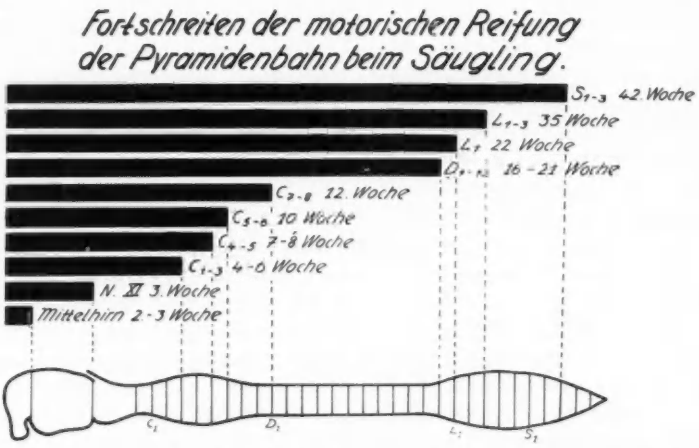

FIG. 1.—Diagram illustrating the development of voluntary movement during the first year of life in terms of the motor supply of spinal segments. From above downwards S1 to 3, 42 weeks, L1 to 3, 35 weeks, L1, 22 weeks, D1 to 12, 16 to 21 weeks, C7 to 8, 12 weeks, C5 to 6, 10 weeks, C4 to 5, 7 to 8 weeks, C1 to 3, 4 to 6 weeks, 11th cranial nerve 3 weeks, mid-brain 2 to 3 weeks (kindly lent by Professor K. Z. Zülch).

which, it will be seen, corresponds closely to our own findings of the caudal shrinkage of the receptive field of the flexor reflex.

(3) The evocation of extensor plantar responses by a cold stimulus from a wide area of the body, including even the neck, though an unexpected finding, is in harmony with Langworthy's observation that the newborn child reacts readily to changes in temperature, especially to

cold, and his statement that the heat and cold pathways are myelinated to the level of the thalamus at birth. The receptive field of this reflex shrinks like that for pin-prick, but more rapidly, and the reflex tends to disappear at the age of about 24 weeks. Heat loss from small babies is rapid on account of their relatively large surface area and the dangers of cooling are now well recognized. It has been shown by Cross, Tizard and Trythall (1958) that the response of the newborn infant to hypoxia differs from that of the adult. In the baby anoxia decreases metabolic activity and therefore leads to a fall of body temperature. This, they suggest, may be a protective mechanism, and they interpret the lack of shivering in babies as a necessary part of this process. Reflex flexion of the lower limbs, however, in response to cold persists for some months and may serve some biological purpose. It would be interesting to know if its disappearance coincides with any change in the baby's processes of heat regulation.

The Receptive Field of the Plantar Reflex in Congenital Diplegia

Having studied the receptive field of the plantar reflex in normal infants we decided next to investigate it in children suffering from lesions of the nervous system present since birth or an early age, and including a number in whom the pyramidal tracts had failed to develop normally. Our material for this investigation consisted of 31 children, 11 seen at the Chelsea Centre for Spastic Children and the remaining 20 at the Fountain Hospital. 13 of these children were under the age of 5, 10 were between 5 and 10, and the remaining 8 were aged between 10 and 15 years. In this group of children there was no evidence that age influenced the abnormalities found. All the children seen at the Fountain Hospital were mentally defective.

The classification of the patients was as follows:

Table II

Congenital diplegia of unknown origin	15
Diplegia associated with microcephaly	5
Diplegia associated with hydrocephalus	3
Congenital hemiplegia	3
Congenital double athetosis	1
Congenital ataxia	1
Tuberous sclerosis	1
Gargoylism	1
Sequel of encephalitis	1

The responses obtained from the various stimuli used are set out in Table III.

The number of single stimuli which produced a response in these 31 patients was 229 and the character of the response is shown in Table IV.

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TABLE IV

Bilateral extensor	100
Bilateral flexor	53
Extensor on side stimulated, flexor on opposite side	33
Extensor on side stimulated, no response on opposite side	20
Flexor on side stimulated, no response on opposite side	15
Flexor on side stimulated, extensor on opposite side	8

Thus in 194 out of 229 instances a single stimulus, whatever its nature, and wherever it was applied, if it produced a response, produced a bilateral one. Cold was rarely effective as a stimulus, producing a response in only 6 cases. In 2 cases it was effective from the upper chest, in 3 from the abdomen, in 4 from the thigh, and in 4 from the sole. A response to pin-prick was obtained the more easily the nearer the site stimulated approached the sole. A plantar response to pin-prick at the level of thoracic 3 was obtained in only 4 cases, on the abdomen in 13, on the thigh in 20 and from the sole in all 31. In several instances (Nos. 1, 7, 13, 16, 17, 20, 22 and 25) a flexor response was obtained by stimulation at a higher level when an extensor response was obtained by stimulating the sole.

The 8 instances in which a stimulus evoked a flexor response on the side stimulated and an extensor response on the opposite side are of special interest, especially the 2 hemiplegics Nos. 4 and 14. In each of these cases stimulation on the normal side evoked an extensor response on the hemiplegic side. The significance of this is considered later. Thus the reflex responses of children with congenital diplegia differ from those of normal infants whose pyramidal tracts have not yet developed. In particular, unlike normal infants, few diplegics show any reflex response to cold, and with few exceptions the extent of their receptive field for the plantar reflex corresponds to that of patients with spinal cord lesions acquired later in life, rather than to that of normal infants. This is illustrated by the following observations.

THE RECEPTIVE FIELD AFTER CERVICAL CORD LESIONS

In order to see whether the receptive field was influenced by the level of the lesion we examined 5 patients with severe, virtually complete, traumatic lesions of the spinal cord at the level of C4 (1), C5 (1) and C6 (3). The results are shown in Table V. Although flexor spasms could easily be evoked in all these patients it will be seen that except for two isolated responses to cold the stimuli we employed were ineffective to elicit extensor plantar reflexes above the groin. The cervical cord lesion, therefore, was not associated with an extensive receptive field. It is, however, a common experience in paraplegia-in-flexion, and was noted in these patients, that sometimes the lightest touch is as effective as a pin-prick in eliciting the flexion reflex of the lower limb.

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The Flexion Reflex of the Lower Limb Elicitable from the Face

CASE REPORT.—Female, aged 42, was admitted to 7520th United States Air Force Hospital on December 14, 1958, under the care of Major M. J. Freedman.

Previous history.—The patient developed rheumatic fever at the age of 5 and had a further attack at the age of 9. A heart murmur was noticed after the first attack. When she was 32 she developed paroxysmal ventricular contractions which would recur when she was active physically or emotionally upset. In March 1953, she developed subacute bacterial endocarditis due to *Streptococcus viridans*. She was treated with penicillin and digitalized for several months. In 1956 she was discovered to have a B.M.R. + 20 and a P.B.I. of 11·5 and 9·4 and a radio-active iodine uptake of 66 per cent. She was treated with antithyroid drugs and on this regime her pulse slowed to normal and she improved symptomatically. The antithyroid medication was discontinued about a year later with no recurrence of her hyperthyroid condition. In 1957 she developed auricular fibrillation and a heart-rate of 150. Quinidine failed to restore her cardiac rhythm to normal and she was therefore maintained in auricular fibrillation, but placed on a maintenance dose of digoxin 0·25 mg. b.d. She did well until she developed numbness and tingling of the left foot, for which she was admitted to hospital.

Physical examination on admission.—The patient was rational and alert. There was slight slurring of speech, and a fine vertical nystagmus in both eyes. There was slight flattening of the left lower face, and some weakness of the left upper and lower limbs. The tendon reflexes were brisk on both sides. The plantar reflexes were, right flexor, left extensor. There was no sensory loss. The patient was fibrillating and showed the signs of mitral stenosis and incompetence, though no signs of heart failure. She was put on anticoagulants.

Subsequent history.—Shortly after admission to hospital the patient became suddenly worse. She fell backwards and her breathing became deep and stertorous. She was unable to speak and to swallow, and there was much frothing at the mouth. She was not completely unconscious, but appeared to be completely paralysed except for her eye movements. The superficial reflexes were absent, the tendon reflexes were brisk on both sides and both plantar reflexes were extensor. Chaddock's and Oppenheim's signs were present on both sides with bilateral ankle clonus.

After several hours her level of consciousness gradually improved and she responded more to stimuli. On the following day it was believed that she was able to hear and had some control over her eyelids. On the ensuing days the control of her eyes and eyelids became more complete. At the time of the onset of the severe symptoms her jaw was strongly closed in spasm and she had a strong sucking reflex. The spasm of the jaw decreased slightly as time went on.

Subsequent examination.—On December 16, 1958, she was seen by one of us (W. R. B.). She was lying motionless with both upper and lower limbs extended. Her respiration was a little rapid, but otherwise normal, Her pulse was completely irregular. The blood pressure was normal. There was a tracheal intubation tube *in situ* and the mouth was closed over it. Her eyes were open and occasional spontaneous movements of the eyes occurred. She was speechless. The optic discs were normal. The pupils were moderately dilated and reacted well to light. She was able to follow the observer's finger when asked to do so to the right, but not quite fully. Conjugate gaze to the left was impaired, but present to a slight extent. She was able to elevate the eyes following the moving finger and depress them. The corneal reflex was present on both sides. Voluntary closure of the eyes on command occurred, but not very strongly and it was still possible to see a little of the sclerotic

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below the lids on either side. She opened the eyes on command. She could evidently hear since she obeyed commands.

In the upper limbs the fingers were gently flexed over bandages and tone was if anything diminished. In the lower limbs tone was possibly slightly increased in the extensors. There was no voluntary movement of the limbs or trunk. The tendon-jerks were all brisk and the plantar reflexes extensor.

Apart from the corneal reflexes the only response to any form of sensory stimulus was as follows. Over the third division of the trigeminal nerve on either side prick caused bilateral closure of the eyes. It also caused ipsilateral flexion of the lower limb on either side with extension of the great toe. This movement could also be elicited from any part of the limbs or trunk on the same side by pin-prick.

Subsequent history.—It was necessary to feed the patient by means of a naso-œsophageal tube, and retention of urine was treated by a self-retaining catheter. The reflex flexion of the ipsilateral lower limb with an upward movement of the toe which at first could be elicited from any part of the body from the cutaneous area of the third division of the trigeminal nerve downwards gradually diminished and the trismus also decreased. The patient was discharged from hospital and returned to the United States by air on January 5, 1959.

Comment.—A female patient aged 42 with long-standing auricular fibrillation developed a left hemiparesis which was suddenly followed by complete bulbar paralysis and quadriplegia. She was conscious and was able to move the eyes and open and close them on command. Immediately after the onset reflex flexion of the ipsilateral lower limb was elicitable in response to pin-prick over the whole of the body from the cutaneous area of the third division of the trigeminal nerve downwards. During the next two weeks the sensitivity to this stimulus gradually diminished. The lesion was thought to be a thrombosis of the basilar artery secondary to embolism.

The reflex response to pin-prick in this case appears to be similar to that observed by Fulton and Keller (1932) in the baboon, and which they termed "monoplegic flexion." They found that "if the motor area, either of arm or leg, is removed, a nociceptive stimulus applied anywhere on the body surface causes abrupt flexion of the monoplegic extremity." Whereas in our patient, whose lesion was bilateral, the response was always strictly unilateral, in the baboon it was "obtained as well from one side of the body as from the other." Fulton and Keller remark that "the response itself, though somewhat quicker, is, interestingly enough, similar to the Babinski phenomenon as seen in the baboon. It is as though the reflexogenous zone had spread from the sole to include the entire body surface."

The Crossed Extensor Plantar Reflex

Reference has been made in the introduction to previous observations on the crossed extensor plantar reflex. We have looked for this in 97 patients suffering from a disorder of the nervous system involving one or both pyramidal tracts. We have classified them as follows:

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(1) Patients with cerebral lesions leading to bilateral extensor plantar reflexes; (2) patients with cerebral lesions leading to a unilateral extensor plantar reflex; (3) patients with spinal cord lesions leading to bilateral extensor plantar reflexes; and (4) patients with disorders causing lesions at both the cerebral and the spinal levels and with bilateral extensor plantar reflexes. The diagnoses were based on the routine clinical examination and any necessary ancillary investigations, but were not confirmed by autopsy. The patients in groups 1 and 2 mostly suffered from cerebral vascular lesions or tumour: those in group 3 from cervical spondylosis or neoplasm of the spinal cord: those in group 4 from disseminated sclerosis. The results are shown in Table VI.

TABLE VI.

			Crossed plantar response in percentages		
	Group	*Total*	*Extensor*	*Flexor*	*None*
1	Bilateral cerebral lesions	27	35·2	22·2	42·6
2	Unilateral cerebral lesions.. ..	14	17·8	28·6	53·6
3	Bilateral spinal lesions	30	15·0	48·3	36·7
4	Cerebral and spinal bilateral lesions	26	9·6	59·6	30·8

These figures show that a crossed extensor plantar reflex is not as exceptional as has been thought, but in the past it has probably rarely been looked for. It occurred in one-half of our patients with congenital diplegia, in one-third of those with acquired bilateral cerebral lesions, but not more than half as often in any other group. This suggests, as other evidence considered below indicates, that supra-spinal centres may facilitate the extensor plantar reflex. The predominant crossed response in those with spinal cord damage, as has often been pointed out, is flexor, part of the crossed extension reflex. When there is doubt whether bilateral pyramidal lesions are cerebral or spinal a crossed extensor reflex is a point in favour of the former. It occasionally happens that a stimulus which elicits a flexor response on the side stimulated evokes simultaneously an extensor on the opposite side. Rarely, in our experience this may happen although direct stimulation on both sides produces a flexor response. In such cases the crossed extensor response is a useful sign if evidence of a pyramidal lesion is not otherwise elicitable. Thus we have not found the crossed extensor plantar reflex especially associated with severe paraplegia-in-flexion, though it was present in 2 out of the 5 patients with severe injury of the cervical spinal cord whom we examined.

EXTENSION OF THE GREAT TOE AS AN ASSOCIATED MOVEMENT

In the course of routine examination of patients our attention was directed to associated movements of the great toe. We observed that

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if a normal person is asked to dorsiflex the ankle against resistance, while keeping the hip and knee extended, dorsiflexion of the toes occurs. If, however, he is asked to flex the hip and knee against resistance, the foot being left free to move, the associated movement of the toes may be either flexion or extension, or there may be little or no movement. We therefore decided to ascertain the relative frequency of these associated movements in normals, and how if at all they were modified by a pyramidal lesion. We investigated this point in 30 normals (Table VII)

TABLE VII.—MOVEMENT OF GREAT TOE IN ASSOCIATION WITH FLEXION OF THE HIP AND KNEE AGAINST RESISTANCE IN NORMALS.

			Flexing R. knee against resistance		*Flexing L. knee against resistance*	
No.	*Age*	*Sex*	*Response on R.*	*Response on L.*	*Response on R.*	*Response on L.*
1	48	F	—	—	—	—
2	34	F	e	—	—	e
3	58	F	e	—	—	e
4	26	F	F	—	—	F
5	18	F	—	—	—	—
6	33	F	—	—	—	—
7	16	F	e	—	—	—
8	51	F	f	—	—	—
9	52	M	e	—	—	—
10	42	M	f	—	—	—
11	13	M	e	—	—	—
12	61	M	—	—	—	—
13	59	M	e	—	—	f
14	45	M	e	f	—	f
15	32	M	e	—	—	—
16	31	M	e	—	—	—
17	32	F	f	—	—	e
18	33	F	f	—	—	e
19	43	F	e	—	—	f
20	41	F	—	—	—	F
21	72	F	e	—	—	e
22	55	F	—	—	—	—
23	39	M	f	—	—	f
24	47	M	f	—	—	f
25	34	M	e	—	—	f
26	58	M	E	—	—	e
27	30	F	F	—	—	F
28	37	F	—	e	—	—
29	27	F	—	—	—	f
30	52	F	E	—	—	E

Abbreviations.—E=vigorous extension. e=slight extension. F=vigorous flexion. f=slight flexion. —=no response.

and in 30 patients with an extensor plantar response on one or both sides (Table VIII). It will be seen that in about one-third of the

TABLE VIII.—MOVEMENTS OF THE GREAT TOE IN ASSOCIATION WITH FLEXION OF THE HIP AND KNEE AGAINST RESISTANCE IN PATIENTS WITH PYRAMIDAL LESIONS. THE LEFT HALF OF THE TABLE SHOWS THE PLANTAR REFLEX IN RESPONSE TO A STIMULUS APPLIED TO THE SOLE: THE RIGHT HALF SHOWS THE MOVEMENT OF THE GREAT TOE IN ASSOCIATION WITH FLEXION OF THE HIP AND KNEE

			Key drag on R.		*Key drag on L.*		*Flexing R. knee*		*Flexing L. knee*	
No.	*Age*	*Sex*	*Response on R.*	*Response on L.*	*Response on L.*	*Response on R.*	*Response on R.*	*Response on L.*	*Response on L.*	*Response on R.*
1	19	F	E	F	E	F	E	e	E	—
2	25	F	e	—	F	—	e	—	f	—
3	55	M	e	—	e	—	—	—	—	—
4	51	M	E	—	e	—	E	—	e	—
5	19	F	E	F	E	F	e	—	e	—
6	29	M	e	—	E	—	—	—	—	—
7	60	F	e	—	E	—	e	e	f	f
8	71	F	e	—	F	—	E	—	—	e
9	13	F	E	—	F	—	E	E	E	—
10	50	M	e	—	e	—	E	E	E	E
11	67	F	e	—	F	—	E	—	e	—
12	67	M	f	—	e	—	e	—	e	—
13	37	M	e	F	e	—	E	—	F	—
14	62	M	E	F	E	F	e	f	F	—
15	44	F	E	F	E	F	E	E	E	f
16	56	M	E	E	F	—	f	—	e	—
17	31	F	E	F	E	F	E	F	E	F
18	68	M	F	—	E	—	—	—	E	—
19	57	M	E	F	E	F	e	—	—	—
20	42	M	E	—	F	—	F	—	F	—
21	45	M	E	—	—	E	E	—	—	E
22	54	M	E	E	E	—	e	E	E	—
23	29	M	E	F	E	—	f	—	f	—
24	58	F	E	F	E	—	E	—	E	—
25	60	F	E	—	F	—	E	—	—	E
26	33	F	F	—	E	—	e	—	e	—
27	63	M	E	—	E	—	E	E	e	e
28	43	M	E	—	E	—	E	—	E	—
29	70	F	E	—	F	—	E	—	E	e
30	59	F	E	e	E	F	E	—	e	—

Abbreviations.—E=vigorous extension. e=slight extension. F=vigorous flexion. f=slight flexion. —=no response.

observations on the normals no movement of the toe was observed, while the remainder were symmetrically distributed on either side of this neutral point in the direction of flexion and extension. In the patients with pyramidal lesions, on the other hand, less than a third showed either no movement or movement in the direction of flexion while more than two-thirds showed a weak or a strong movement of extension of the great toe.

From these observations it would appear that while flexion and extension of the great toe are equally frequent as normal associated movements accompanying flexion of the hip and knee against resistance, a pyramidal lesion tips the scale in favour of extension. And if we may assume that the patients with pyramidal lesions had prior to their lesions a normal distribution of flexor and extensor components of the associated movement we must conclude that in about a third of these cases the effect of a pyramidal lesion was to convert the associated movement of the great toe from either a flexor or a neutral response into an extensor one.

Normal and Abnormal Flexor Plantar Reflexes

The normal flexor plantar reflex.—Apart from some modification of details little alteration has been made in Collier's (1899) original account of the normal plantar reflex, which he interpreted as the response best adapted to the contact of the sole of the foot with an irritating object in the course of plantigrade progression. Fulton and Keller (1932) state that plantar flexion is the normal response to stimulation of the sole in the intact monkey. In the baboon the response is said to be uniformly sluggish, but predominantly flexor in type. In the gibbon the reflex is normally flexor, and the same is true of the chimpanzee. Fulton and Keller noted in both the baboon and the gibbon that, if the animal was struggling, extension of the hallux might occur in association with flexion of the hind-limb. And in the chimpanzee, they wrote, "occasionally when the animal is about to flex his hind extremity, as in preparation for climbing, stroking or pinching the sole of the foot will give rise to an extension of the toes with abduction of the hallux. Such a response is seldom seen, but it is unmistakable when it occurs and is undoubtedly due to an alteration in the higher control of the lower centres in preparation for the execution of a withdrawal movement. The stimulus to the sole in these circumstances serves to precipitate the withdrawal movement." Apart from these exceptions, upon which we shall comment later, it would seem that the flexor plantar reflex is the normal response to a nocuous stimulus applied to the sole in monkeys and all the primates.

The flexor plantar reflex in early infancy.—As we have seen, several workers, Minkowski (1927), Waggoner and Ferguson (1930) and

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Schlesinger (1927), have noted that during the first few weeks of life in some human infants the normal plantar response may be flexor.

The flexor plantar reflex during spinal shock.—Holmes (1915) and Collier (1916) first noted a flexion-adduction movement of the toes as the earliest reflex response after severe damage to the human spinal cord, and Riddoch (1917) made the same observation in cases of complete cord transection. Sherrington (1898) stated that in the monkey in some instances after transection below the region of the brachial enlargement an unusual "status" supervenes, during which almost always the earliest skin reflex elicitable from the isolated spinal cord is "adduction-flexion of the hallux, elicitable by stimuli applied to the third, fourth, or fifth digits (plantar surface or sides), or to the skin of the sole, especially of the fibular side." On this Sherrington makes the interesting comment: "Not a little surprising is it to find that the movement which, on account of its being the most easily evoked and the one evoked alone when depression of reflex activity is great, may be called the primary spinal reflex of the limb, is the very movement which has often been urged to be *par excellence* the most eminently cortical one—namely, flexion-adduction of hallux." Fulton and Keller have confirmed Sherrington's observations on the monkey and the baboon.

Flexor plantar responses with long-standing pyramidal lesions.—In some of the cases of spastic diplegia a stimulus applied at a higher level, for example the chest in No. 6, the abdomen in Nos. 8, 10, 17 and 18, elicited a flexor response when an extensor response was elicitable by stimuli applied at lower levels. A similar observation was made in some of the normal infants.

Thus it would seem that at the lowest functional level of spinal cord activity, when all other spinal functions are depressed, there exists a rather feeble flexor reflex of the toes in response to a stimulus applied to the sole, which Holmes describes as a "unisegmental reflex response, in muscles supplied by the first sacral segment, which also receives the impulses originated by the stimulus applied to the sole."

The Receptive Field of the Plantar Reflex

The receptive field in infancy.—As our observations show, in the young infant a plantar reflex can be elicited from a large area of the body, sometimes including the neck. The receptive area shrinks progressively, especially after the age of 21 weeks. Since the shrinkage occurs from above downwards it is reasonable to correlate it with the downward progress of myelination, especially of the pyramidal tracts. These changes, observed during the first year of life, may be interpreted as the progressive development of local signature. Here a parallel restriction takes place in the motor response to that manifested in the

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narrowing of the receptive field. A reflex which during its phase of highest activity consists of a bilateral response in the lower limbs to stimuli applied over a large part of the body becomes progressively restricted to the response of one lower limb only to a stimulus applied to an area limited to its distal segment.

The receptive field in pathological conditions.—We have little to add to previous observations on this point. Our main conclusion is the negative one that the state of affairs found in normal infants is not paralleled in patients suffering from lesions of the nervous system. Whether these are congenital and result in severe diplegia, or acquired, and produce severe damage to the spinal cord, even at the highest level compatible with survival, the receptive field rarely extends above the abdomen and is most often limited to the lower limbs. Similarly after lesions of the nervous system cold is rarely effective as a stimulus, being so in only 6 out of 31 cases of congenital abnormality, but in 4 out of 5 of our patients with cervical cord lesions some reflex response to cold was obtained from one or other sole.

Our patient, in whom an ipsilateral flexor withdrawal reflex of the lower limb could be elicited from any part of the body as high as the lowest one-third of the face, is therefore quite exceptional and suggests that some favourable circumstance, perhaps related to the site of the lesion in the brain-stem, temporarily favoured a wide irradiation of the reflex response to a nocuous stimulus. In what appears to be the parallel case of the baboons observed by Fulton and Keller the lesion again was at a high level, in that instance removal of the motor area.

The Extensor Plantar Reflex in Relation to the Functions of the Pyramidal Tract

We take it as established that the extensor plantar response is a sign of undeveloped or impaired function of the pyramidal tract, though it has long been clear (Walshe, 1914) that the flexor reflex of the lower limb is normally under extrapyramidal control as well, and only appears with its full force when descending spinal pathways additional to the pyramidal tracts are damaged.

The observation that the extensor plantar reflex is part of the flexion reflex of the lower limb, that it is homologous with the nociceptive flexion reflex of the spinal animal and that in both cases it is manifested after a lesion of corticospinal pathways, has perhaps too readily been interpreted as meaning that the extensor plantar reflex, and perhaps the flexor withdrawal reflex of which it is a part, are to be regarded *merely* as "release phenomena," making their appearance only when some normal inhibitory influence is withdrawn. There is much evidence for the inadequacy of this view.

A flexor withdrawal reflex of a limb may occur in response to a

nocuous stimulus in a normal animal. It is a common experience too in normal people, as pointed out by Riddoch (1917), that a sharp and sudden stimulus to the sole may cause a withdrawal movement of the whole lower limb, in which flexion of the toes is followed by extension of the great toe, and the clinician is accustomed to distinguish this from a pathological extensor plantar reflex. Thus the pattern of the flexion reflex of the lower limb can be regarded as lying latent in the normal individual. But it may be thought that the normal plantar reflex with flexion of the great toe differs in kind from the flexion reflex of the lower limb of which extension of the great toe is a part, and which follows a pyramidal lesion. Our observations on the associated movements of the great toe show, however, that a parallel change can be detected in the pattern of voluntary movement after a pyramidal lesion. We observed much variability in the character of the movement of the great toe accompanying flexion of the hip and knee against resistance, but extension of the hallux can be regarded as normal in such circumstances, since it occurred in about one-third of the controls. The effect of a pyramidal lesion, however, was to increase the frequency with which this associated movement occurred. The upward movement of the great toe reported by Fulton and Keller in struggling animals may well have been an associated movement rather than part of the reflex response to stimulation of the sole.

The experimental observations of Sherrington, confirmed by those of Walshe and Riddoch in man, have demonstrated the existence of complex reflex patterns in the spinal cord, such as the crossed extension response of the lower limb opposite to the one from which a flexion reflex is elicited, spinal stepping etc., and Sherrington showed that in the decerebrate animal the elicitation of a flexion reflex may modify the posture of the whole of the rest of the body and even excite a pseudo-affective response. Thus the evidence suggests that the organization of many of the simpler and more automatic motor activities exists at the bulbospinal level, and that it is these which we sample in a crude manner when we demonstrate their existence as reflexes after lesions which remove the control of higher levels.

We earlier quoted Sherrington's observation that the movements most easily evoked from the spinal cord when depression of reflex activity is great are the movements which are "most eminently cortical." Sherrington observed that this "large and predominant representation in the cortex is concomitant with, rather than in contrast against, a large and predominant representation in the spinal cord." Thus he clearly envisaged a physiological link between cortical representation and the organization of movements at the bulbospinal level.

The classical study of stimulation of the motor cortex by Leyton and Sherrington (1917) yielded some observations which are highly relevant

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to our thesis. In stressing the functional instability of cortical motor points, whereby the response elicited by stimulation of a single point might be profoundly modified by stimulation of other points, the authors illustrated this by means of some observations on the elicitation of movements of the lower limbs: "Point 331, which evoked flexion of the knee when stimulated in quick succession to point 342, evoked when stimulated in quick succession to point 263 extension of hallux, the regular response from 263 itself being extension of hallux followed by extension of the remaining toes, followed further by dorsal flexion of ankle, and finally by flexion of hip."

Here, then, the very succession of movements which characterize the flexion reflex of the lower limb is elicitable by stimulation of the motor cortex, and preliminary stimulation of the point which evokes this movement facilitates its evocation from a point, stimulation of which had previously evoked only a fractional part of it.

A similar observation has been made in man, for Bates (1953), studying the effect of stimulation of the medial aspect of one cerebral hemisphere after removal of the other in cases of infantile hemiplegia, noted that in 5 cases cortical stimulation evoked an upward movement of the great toe on the ipsilateral, hemiplegic, side; and in 2 cases "a withdrawal of the lower limb with up-going great toe was produced on the hemiplegic side from cortical stimulation," but these, of course, were not normal individuals. Sherrington and Leyton draw the following conclusion concerning the relationship between cortical motor function and the organization of movements of the bulbospinal level:

> "A property possessed by the cortex is the combining of a large, though exhaustible, number of movements, belonging to this and that restricted portion of limb, face, or other motile part, into sequences of very great variety, sequences in which members of the same group of elementary movements follow now in one order, now in another, according as the point of cortex stimulated is chosen now at one place or now at another not too far apart, and influenced also by the stimulations that have been more immediately precurrent. . . . From movements of locally restricted parts—e.g. movements of a finger or of a limb-joint (movements themselves discrete and individually separable in the motor cortex)—the upbuilding of larger combinations varied in character and serviceable for purposes of different and varied kind, prehensile, defensive, locomotor, mimetic, masticatory, deglutitional, orientational (in von Monakow's sense), etc., is one of the main offices performed by the motor cortex. The functional properties of this cortex seem specialized for that end. . . . How does the motor cortex obtain these fractional and partial movements on which work its powers of varied synthesis? Simpler co-ordinated elements, such as flexion of a single joint—e.g. knee or elbow—can be safely assumed to lie ready to its hand in the bulbospinal mechanisms. But the higher of the compounded movements which those mechanisms give tend, if judged from the spinal and decerebrate dog and cat, to be compounds exhibiting total flexion or total extension of a whole limb. In the limb movements evoked from the anthropoid motor cortex, flexion of one joint may go either with flexion or with extension of another. The motor cortex may

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therefore obtain the partial and fractional movements it so variously weaves together by, to a certain extent, breaking up compounds already constructed by lower centres. Such analytic power may be a property of its own, or some other, perhaps subcortical, organ with which it keeps close touch. Such synthesis involves time adjustments as well as spatial adjustments. The bulbospinal axis also, of course, synthesizes motor acts. But the difference between the constructive planes of the two is considerable. Bulbospinal synthesis constructs in the main those locally restricted but co-ordinate movements which the cortical synthesis finds ready to hand as elements for it to work with. . . . But comparison of the synthetic capacity of the bulbospinal organ with that of the motor cortex reveals a great excess of synthetic capacity in the latter, as evidenced by the variety and the multiform scope of the motor acts and sequences it builds up. . . . What has been termed above the "functional instability" of cortical motor points seems but one aspect, revealed to experiment, of the many-sided motor synthesizing which this cortex can effect."

The evidence in favour of the nociceptive nature of the flexion reflex of the lower limb has recently been reviewed by Walshe (1956). But, as he admits, "when the flexion-reflex is extremely powerful . . . the reflex is so facile that the lightest stroke or even touch on the sole will fire it off." The fact that the reflex may be elicitable by a non-nocuous stimulus requires explanation. It is notable that this occurs only in cases of complete, or nearly complete, division of the spinal cord: it is not a characteristic of the average case in which an extensor plantar reflex is obtained. The conditioning of reflexes mediated by the divided spinal cord has received little attention, but there is evidence that its responses are sufficiently plastic to be capable of considerable modification by treatment instituted sufficiently early after injury. The development of a flexion reflex in response to touch in long-standing cases of paraplegia-in-flexion is not, therefore, a conclusive argument against its fundamentally nociceptive character.

In conclusion let us go back to our observations on the plantar reflex in the normal infant. As we said earlier, it would be unphysiological to identify the normal too closely with the pathological. There are various possible anatomical and physiological interpretations of the readiness with which the flexor reflex of the lower limb can be elicited in infancy, but it is perhaps not unreasonable to assume that the fact that this reflex is present at birth, and persists in some degree for at least a year, is because it possesses some biological value. This view is supported by the further fact that for half of the first year of life the reflex can be elicited by cold. It seems probable that at least to some extent the gradual shrinkage of the receptive fields of the flexion reflex from above downwards during the first year of life is due to the progressive centripetal myelination of the pyramidal tracts during this period. Since the pathological extensor plantar reflex is to be regarded as primarily a symptom of the withdrawal of the influence of the pyramidal tract, it seems likely that the functional development of these tracts during the

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first year of life leads to inhibition of those reflexes through which it can be elicited from the greater part of the body surface, progressively from above downwards. In this way pyramidal function confers upon the plantar reflex local sign, which is manifested in the narrowing of the receptive field and of the motor response, in which moreover plantar flexion of the great toe now prevails over extension. Acquired lesions of the pyramidal tracts reverse this process. (There is, of course, as many workers have shown, some degree of local sign even in reflexes mediated by the distal portion of the divided spinal cord.)

However, the differences between the pathological flexor withdrawal reflex and the normal infantile one are at least as great as the resemblances. The differences, to which we have drawn attention, indicate that neither pyramidal damage alone nor complete division of the spinal cord produces a condition physiologically resembling that found at any stage of normal development. The development of the nervous system during infancy exhibits the organization of myelination on a time-scale in which growth of motor and shrinkage of reflex activity proceed *pari passu*, preserving throughout the balance of normal biological function, including normal muscle tone. The presence at birth of myelination in the sensory pathways up to the thalamus suggests that the wide receptive field for the flexion reflex of the lower limb in the early months of life, and especially the response to cold, may depend upon facilitation at supraspinal levels, in much the same way as the abdominal reflexes are normally regulated by a cerebral outflow (Hagbarth and Kugelberg, 1958). This may explain why such a wide receptive field is not usually encountered after complete transection of the spinal cord, and perhaps also why it occurred in our patient with the brain-stem lesion.

Our observations on associated movements of the great toe in normal individuals and after a pyramidal lesion show that the difference between the pathological flexion reflex of the lower limb of which the extensor plantar reflex is a part, the normal flexor plantar reflex, and a voluntary movement of flexion of the lower limb is not a difference of kind, but rather of physiological organization, the pathological flexor withdrawal reflex being in Jackson's phrase the most organized and the most automatic. Here we can see at work the cerebral cortex, as Walshe puts it, "using the pyramidal system as the pathway by means of which it achieves a fractionation and combination (in time and in space), by processes of selective inhibition and excitation of bulbospinal motor mechanisms, of those reflex synergies that the experimental study of the variously truncated nervous system has revealed to us in such abundance" (Walshe, 1948).

Summary

(1) The plantar responses to various stimuli have been studied in 35 normal infants.

(2) In children up to the age of 8 days the plantar reflexes were almost always extensor. They could often be elicited to pin-prick or cold as high as the 3rd thoracic segment.

(3) Children aged between 5 and 20 weeks showed the greatest activity of the reflex. A bilateral extensor response could be obtained from the sole, and the thigh. A response obtained from the abdomen or chest was almost as often flexor as extensor.

(5) With one or two exceptions cold ceased to be effective as a stimulus at the age of 24 weeks.

(6) It is suggested that the shrinkage of the receptive field in infancy is related to the centripetal myelination of the pyramidal tracts.

(7) The findings in the normal infant are compared with observations made on 31 children suffering from lesions of the nervous system present from birth, and with 5 adult patients suffering from severe lesions of the spinal cord at the cervical level.

(8) The case is reported of a patient with a brain-stem lesion in whom for a time an extensor plantar response could be evoked by pin-prick applied to any part of the body from the lower one-third of the face downwards.

(9) The crossed extensor plantar reflex, i.e. an extensor response as a result of a stimulus applied to the opposite sole, has been looked for in 97 patients with lesions of the brain and spinal cord. It was found most frequently (35·2 per cent) in those with bilateral cerebral lesions and least frequently (9·6 per cent) in those with both cerebral and spinal lesions.

(10) Extension of the great toe as an associated movement has been studied, and it has been found that while extension of the great toe may occur in normals in association with flexion of the hip and knee it occurs more frequently in patients with a pyramidal lesion.

(11) Some pathological conditions in which in spite of pyramidal damage flexor plantar reflexes may occur are reviewed.

(12) The observations reported in this paper are discussed in relation to the functions of the pyramidal tract, and it is concluded that the difference between the pathological flexion reflex of the lower limb of which the extensor plantar reflex is part, the normal flexor plantar reflex, and a voluntary movement of flexion, is not a difference of kind but of the nature and degree of physiological organization exhibited.

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THE PLANTAR REFLEX IN MAN, WITH SPECIAL REFERENCE TO SOME CONDITIONS WHERE THE EXTENSOR RESPONSE IS UNEXPECTEDLY ABSENT[1]

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INTRODUCTION

THE discovery of the sign of Babinski (1896, 1898) at a time when presently held concepts of the neurone doctrine and the spinal reflex were still new, led inevitably to bitter controversy lasting a decade or more. Nevertheless the sign survived as a singularly useful manœuvre of the neurological examination, and its significance and validity, if not its utility, have not been questioned again until recently (Lassek, 1954; Nathan and Smith, 1955; Boshes, 1957). Recently, also, Walshe (1956) has risen to the sign's defence. Further investigation, activated by the resurgence of past doubts, must start from the premises, the methods of examination, and the conclusions drawn by the initial investigators. Walshe (1914) put forth a view which is still generally accepted:

"Of this reflex flexion, dorsiflexion of the hallux is an integral and inseparable part, and this constitutes the 'extensor' type of plantar response, the Babinski toe phenomenon, the appearance of which is recognized to be pathognomonic of pyramidal tract affection.

"The 'extensor' response is, therefore, part of the flexion reflex, and analysis proves it to be an integral part of this, never occurring without reflex contraction of the proximal limb flexors.

"According to Marie and Foix, and in this respect my observations would tend to confirm their view, the normal plantar response is a unisegmental reflex strictly comparable with the abdominal and cremasteric reflexes, and involving no co-ordination whatever, that is, no reciprocal innervation; it disappears in pyramidal lesions, being replaced by a *new* reflex, which is not purely cutaneous and which is a co-ordinated movement, namely the flexion reflex. In the normal plantar reflex we see on stimulation of the first sacral segmental skin area, a simple contraction of muscles innervated from this segment; the short flexors of the digits and tensor fasciæ femoris.

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"I have described the variability of the contractions of the adventitious muscles in the 'flexor response,' and the participation in the movements of muscles belonging to both flexor and extensor groups. I would further draw attention to the extremely limited receptive field of the normal reflex and to the fact that it is indeed a cutaneous reflex pure and simple. *It differs fundamentally, therefore, from the pathological plantar response*" [italics ours].

Thus the two types of plantar reflex are identified as *different* and *discrete* phenomena.[1]

The normal flexor plantar response has received much less attention. The classical teleological evaluation is that of Collier (1899):

"The economic significance of the nature of this reflex is clear. In plantigrade progression, if an irritating object comes in contact with the sole of the foot, the flexors of the hip acting at greater mechanical advantage as regards range of movement than any other muscle, will be best adapted to remove the foot from the offending object; the foot is fixed by dorsiflexion of the ankle, and the whole surface is at once removed from the ground while the flexion of the toes and the inversion of the foot render the skin of the plantar region lax, so that any sharp object will penetrate less readily. . . . I propose to call this normal form of plantar reflex characterized by flexion of the toes and marked early action of the tensor fasciæ femoris as the 'flexor response'."

Although the view is widely accepted that these two reflexes, admittedly conflicting in transitional states, are independent muscular synergic patterns, it is generally believed that they are both adaptive responses to nociceptive stimulation. A further distinction between them was drawn by Riddoch (1917):

[in spinal shock] "One of the earliest reflex reactions to appear is a downward movement and adduction of the hallux in response to a scratch applied to the sole of the foot. . . . Finally, the toe-movement gradually changes in direction from 'flexion' to 'extension,' and the typical flexion reflex with an up-going toe is then the only response evoked by nocuous stimulation of the sole.

". . . A downward movement of the toes forms part of the general extension of the limb in the first phase of step, and it is by far the most common toe-movement employed by the normal individual. It is also the characteristic response to a light scratch or prick applied to the skin of the sole, and since, with the nervous system intact, inhibition is at its highest, it forms the only movement of the limb. When, however, the affective stimulus is intense and is applied without warning, and especially if the individual is oversensitive to pain, a withdrawal movement of the whole limb may ensue, and brief downward movement of the toes is followed by upward movement. That is to say, inhibition has been broken through for the movement by the sudden application of a harmful stimulus, and *a protective reflex, analogous to that at the spinal level is evoked as the end effect* [italics ours].

[1]The clinical extensor (dorsiflexor) reflex, named anatomically by the more forceful toe muscles active in it, is thus identical with the physiological flex*ion* reflex which withdraws the foot from the stimulus at ankle, knee, and hip. The clinical flex*or* (plantar flexor) response, also named on anatomical ground, may or may not be an extension reflex in the sense of a supporting or thrust reaction. In this paper "flexor" (plantar flexor) and "extensor" (dorsiflexor) refer specifically to hallux movement.

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"Compare this reaction with that which occurs when the reflex arcs of the lower extremities are separated from cortical control by injury to the spinal cord, and at a time when reflex excitability in the portion distal to the lesion has returned. A stimulus just liminal can no longer excite a response limited to the toes. Contraction of all of the flexors of the limbs together with upward movement of the toes, invariably occurs and, when the spinal transection is complete, the flexion reflex can be studied in all its extravagance. 'Local signature' has been destroyed. The unit protective reaction of a central nervous system, which is entirely spinal, involves the whole limb, and is never confined to a part of the limb."

The present study provides a clinical and electromyographic evaluation of both normal and abnormal plantar reflexes. We shall conclude that these are not separate phenomena, but rather quantitative and spatial variations of a common pattern.

Material and Methods

The 14 normal subjects were laboratory personnel without history or physical findings of neurological disease. Their ages varied between 20 and 68 years. The pathological cases showing extensor reflexes were chosen from in-patient services because of the vigour and consistency of their reflex behaviour. There were 12 patients in this group whose diagnoses included middle cerebral artery thrombosis, anterior cerebral artery thrombosis, multiple sclerosis, traumatic paraparesis, hereditary spastic ataxia, and paraparesis of unknown cause. The acute paraplegic patients included all those admitted by the neurosurgical service during the period of this study in whom it was reasonable to believe that spinal cord transection was functionally complete.[1]

Several cases were selected for study because they had transitional plantar reflexes. Some cases of chronic traumatic paraplegia and amyotrophic lateral sclerosis were also examined.

All subjects were examined in a supine position. Electromyographic and 16 frame/second motion picture records were made in sequence on the same day.

Electromyographic observation was limited to those muscles most prominently active, and particularly those concerned with movement of the hallux. A complete survey of muscles responding in the reflex was not attempted. Most muscles were recorded with skin electrodes. These were 0·5 cm. silver cups coated with electrode jelly and attached with adhesive tape about 3 cm. apart in a longitudinal direction. Various functional tests indicated that spread of action currents from distant muscles was not significant.

An experimental limitation pointed out by Kugelberg (1948) is set by the pain from insertion of needle electrodes. Penetration of the fascial structures in the leg and foot may be quite painful, particularly during vigorous movement. Thus the recording electrode may produce spurious stimulation. Superficial procaine injection was sometimes helpful. Movement artifact was also a problem.

Preliminary studies in normal subjects indicated that flexor hallucis longus is usually less active in the flexor response than are the short hallux flexors, and since the former muscle is an awkward one to approach it was not studied subsequently. Extensor hallucis longus, on the other hand, proved to be of critical importance, and it was examined routinely in all subjects. Its identification by electromyographic means was not always easy. The electrode was inserted to the medial surface of the middle third of the fibula. Confirmation of placement was obtained from movements on command where possible, from mechanical displacement of the needle by

[1]We are indebted to Dr. H. G. Schwartz and the neurosurgical staff.

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passive toe movement, and from electrical stimulation through the recording electrode. The last proved less reliable than we had anticipated, for on one occasion we found that the closest motor point was that for the extensor of the second toe when by the other criteria the needle tip was obviously in extensor hallucis longus. Double core concentric needles were used to obtain optimal localization of motor unit activity (Landau, 1951).

The medial plantar muscle bundle includes flexor hallucis brevis, abductor hallucis and adductor hallucis. Their combined function includes primarily flexion at the metatarsophalangeal joint and bracing of the plantar arch. This muscle group, tibialis anticus, and the semitendinosus-adductor complex were recorded in almost all subjects. For the last, the leads were placed on semitendinosus, but the adductor group was immediately adjacent. In addition, extensor digitorum longus, extensor hallucis brevis, and tensor fasciæ latæ were examined in many cases.

Potentials were amplified through capacity coupled stages and were photographed from a dual beam cathode ray oscilloscope. Mechanical stimulation was produced with the point of a safety-pin. The moment of contact was signalled by connecting the pin to a battery-capacity-resistance circuit and an indifferent electrode on the patient. The plantar surface was coated with electrode jelly to improve electrical contact. Gradation of stimuli was obtained largely by varying the pressure of the pin. Stimuli were limited to the lateral plantar surface and the lateral surface of the foot. The electrical stimuli (1 msec. pulses, 100/sec.) were applied with 1 mm. metal electrodes 3 mm. apart attached to the lateral plantar surface with adhesive tape.

The stimulus and the afferent pathway.—It has been reported many times that the prepotent stimulus to the lateral plantar surface is a painful one in both abnormal and normal subjects, although only the former have been studied carefully in recent years (Kugelberg, 1948). Landau and Bishop (1953) observed that a high voltage repetitive shock applied to the skin produces a pure sensation of pricking pain. Applied through a light wire moving across the sole, we found that the stimulus elicited a typical flexor reflex in the normal, and an extensor one in the pathological subject (the wire contact alone was not perceived). However, a moving object which applies blunt pressure to the sole may be an adequate stimulus for a normal subject even though it does not produce an uncomfortable degree of pain. A very light pressure can elicit an active pathological extensor response. One may therefore question whether non-nociceptive stimuli can of themselves be adequate, and whether adequate stimuli and afferent pathways differ significantly for the two reflex patterns.

Spinal anæsthesia offers a method for differential block of afferent nerve fibres, the larger ones (which do not subserve pain conduction) being more resistant to this agent (Heinbecker, Bishop and O'Leary, 1934). During the induction of spinal anæsthesia we examined 4 neurologically normal subjects and 3 abnormal ones who had extensor plantar reflexes.[1] 2 of the latter had unilateral extensor reflexes, presumably due to cerebral vascular lesions. The other had bilateral extensor responses due to an unverified spinal lesion. Reflexes and

[1]We are indebted to Dr. Robert Dodd and the Division of Anesthesiology.

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motor and sensory function were followed after the intrathecal injection of 6 to 10 mg. of Pontocaine.

Without exception the plantar reflexes to maximal stimulation were abolished in all subjects at least 4 to 12 minutes before any deficit could be detected in proprioception, light touch, and vibration perception, or in movement. Pin-prick (conveyed over smaller fibres) was invariably diminished to absent at the time when the reflex disappeared. There was no difference between the survival of flexor and extensor responses in the patients who had both, nor did the time course in the patient with bilateral Babinski responses differ from that in the normal subjects.

The plantar reflex is thus related to pain perception and not to that of proprioception, touch, and vibration. The latter senses are served predominantly by large myelinated fibres.

The ankle-jerks also disappeared before proprioception (Sarnoff and Arrowood, 1947) and at approximately the same time as the plantar reflexes, occasionally preceding them. However, this seems to be due to block of the small gamma muscle efferents which sensitize the muscle spindle tension receptors (Matthews and Rushworth, 1957*a* and *b*); the excitability of the receptor organs is thus depressed. It is possible that this suppression of tonic proprioceptive afferent discharge also adds to the depression of the plantar reflex. Nevertheless it is clear that flexor and extensor responses share predominant dependence upon thin fibre nociceptive pathways.

Further evaluation of the afferent pathway involved the measurement of response latencies. For both normal and pathological conditions the latency following the application of a moving sharp object to the skin was never less than 90 msec. Using a high voltage single shock we found, as did Kugelberg (1948), that effective responses were often difficult to elicit. With a stationary electrode and 1 msec. repetitive shocks at 100 per second, the responses occurred readily after 3 to 6 shocks with latencies from the first of 70 to 110 msec. for both normal and pathological reflexes (fig. 1A, B, C). These latencies could be accounted for by summing afferent conduction time in delta fibres with efferent conduction time in alpha fibres and adding a few msec. more for synaptic delay.

In normal subjects the reflex response latency to the maximal tolerated electrical tetanus of the planta was measured 30 to 90 min. after application at the ankle of a blood pressure cuff inflated to 250 mm.Hg. When delta fibre pricking pain was abolished (Landau and Bishop, 1953), the reflex latency in the normal subjects of this study increased to 400 to 1,200 msec., values compatible with C fibre conduction rates (fig. 1D, E). A similar range of delays occurred in the extensor reflexes of patients studied by the same technique (fig. 1F, G). In both cases the threshold of electrical stimulation often rose. Our findings differ from Kugelberg (1948) in that he did not find C fibre latencies lower than 1 second. It

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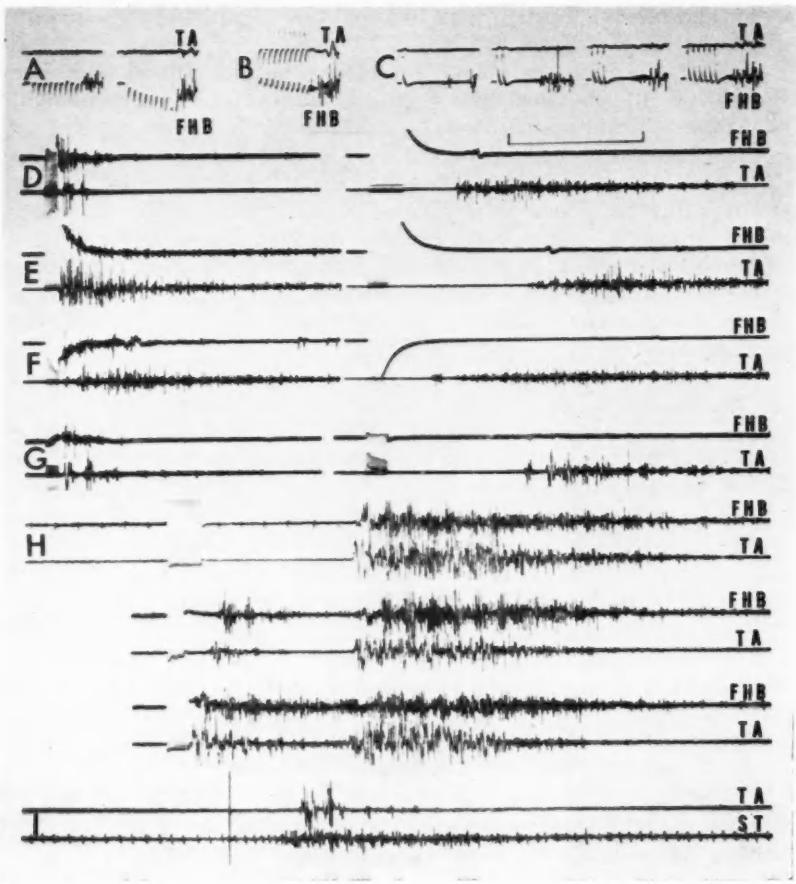

FIG. 1A–C.—Electric shocks to planta at 10 msec. intervals. A, Normal subject. Suprathreshold and maximal tolerated responses. Note the lower threshold for the hallux flexors. B, Extensor reflex in patient with old traumatic paraparesis, maximal stimulus. Note shorter latency of hallux flexors. C, Effect of temporal summation. Extensor reflex, chronic paraplegia (Case 6). Note the augmentation of the hallux flexor response without significant shortening of latency, and the recruitment of tibialis anticus, as the number of shocks is increased. This case had the shortest latency measured. D, Normal subject. Maximal 100 per second tetanus to planta before block and 49 minutes after application of 250 mm.Hg. blood pressure cuff to the ankle. Note that the hallux flexor response disappears because the nerve block is proximal to the muscle. After block the duration and intensity of the stimulus had to be increased in order to obtain the delayed tibialis anticus response. E, Normal subject as in D showing delay of response 60 minutes after cuff application. F, Paraparesis of unknown cause with extensor toe sign. Reflex delay as in D and E

may be concluded that both normal and pathological plantar responses are served by C as well as by delta pain afferents.

Following electrical stimulation the biphasic extensor response that Kugelberg assigned to separate activation of delta and C afferent volleys was seen distinctly in only one patient (fig. 1H), but a suggestion of it was noted in several others. We have no explanation of the lower electrical threshold of the C fibres. The biphasic pattern was not seen in response to mechanical stimulation.

As clinical experience demonstrates, both temporal and spatial summation are of great importance in mechanical stimulation. That the excitatory state of the spinal cord builds up preceding active movement in the extensor reflex was demonstrated in a few patients where single motor units were active at a regular rate before the stimulus was applied. The discharge rate of such motor units might accelerate for several hundred msec. before the active co-ordinated movement took place (fig. 1I).

The only stimulus areas explored routinely were upon the lateral surface of the planta and the side of the foot. In normal subjects the flexor response activated from the latter tended to have a higher threshold and to show a less vigorous flexor contraction. Often there was no significant variation in response with change in the locus of stimulation. Similarly in most cases where the extensor reflex was fully developed, the pattern of movement was practically independent of this limited variation of stimulus site. A tendency toward toe flexion and foot inversion with medial plantar stimulation was noted by Babinski (1898), while Sherrington (1898) observed variation of response with stimulus site in the spinal monkey.

Reflex variations that were dependent on the stimulus site are described below.

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90 minutes after cuff application. G, Same patient as B. Delay in response 53 minutes after cuff application. H, Multiple sclerosis with extensor reflex. First trace shows a threshold (C fibre) response after a latency of more than a second. Note that a motor unit tonically active before the stimulus is not accelerated. Second trace shows a response to a stronger stimulus with an early (delta fibre) response which comes still earlier when the same intensity tetanus is prolonged (third trace). I, Mechanically elicited extensor response in a case of anterior cerebral artery thrombosis. The vertical line signals when the stimulus touched the skin. Note the gradual acceleration of the semitendinosus motor unit before the active movement complex takes place. The electrical artifact produced by the contact of mechanical stimulation is uniformly retouched as a vertical line in all figures. Time base is 1 second. Muscle name abbreviations are: ADD—thigh adductors; EDL—extensor digitorum longus; EHB—extensor hallucis brevis; EHL—extensor hallucis longus; FHB—short hallux flexors; GA—gastrocnemius-soleus; PS—paraspinal; RF—rectus femoris; ST—semitendinosus; TA—tibialis anticus; TFL—tensor fasciæ latæ.

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The Normal Flexor Response

The usual pattern included early strong contraction of the short hallux flexors with an associated response in the foot dorsiflexors (fig. 2A). Extensor hallucis longus was always silent (fig. 2B, C) with the exception that in some subjects a few late "recovery" potentials were noted after the primary response had occurred.

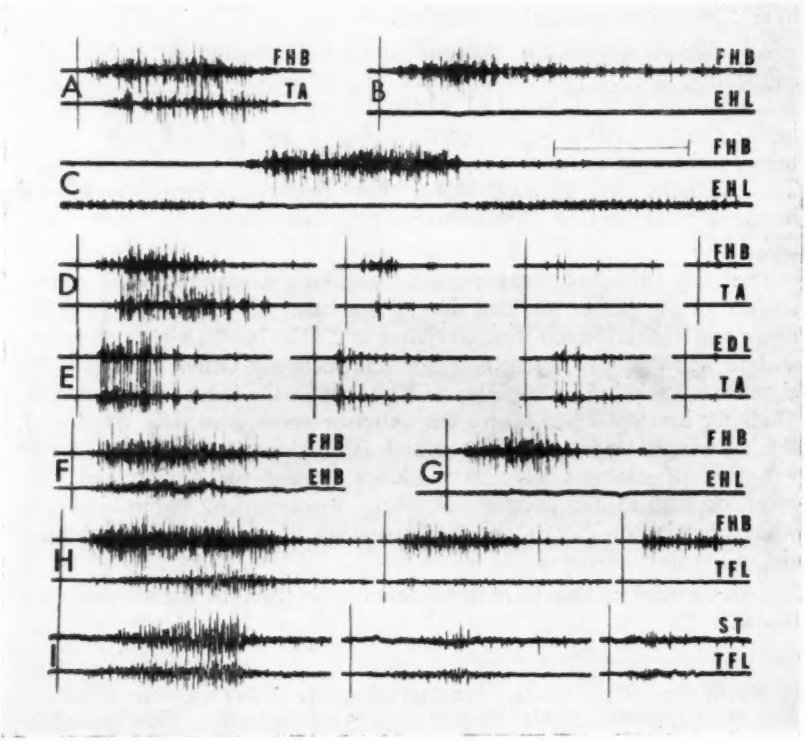

FIG. 2.—Normal flexor response. A–C, Same subject. Extensor hallucis longus, which is silent in the plantar response in B, is active during alternate extension and flexion of hallux on command in C. D–I, Another subject. Records are arranged to show effect of decreasing intensity of stimuli in order to determine the relative thresholds. Description in text.

Graded stimuli almost always showed a lower threshold for the great toe flexors than for tibialis anticus (fig. 2D). The latter muscle was never lower. The extensor digitorum longus contraction always showed a similar threshold and contraction pattern to that of tibialis anticus (fig. 2E). Similarly, extensor hallucis brevis accurately reflected hallux

flexor contraction, by contrast to the silent extensor hallucis longus (fig. 2F, G).

Though tensor fasciæ latæ was prominent in the flexor reflex, it was always possible to show that its threshold was significantly higher than that of the hallux flexors (fig. 2H). Usually tensor fasciæ latæ and semitendinosus responded together (fig. 2I).

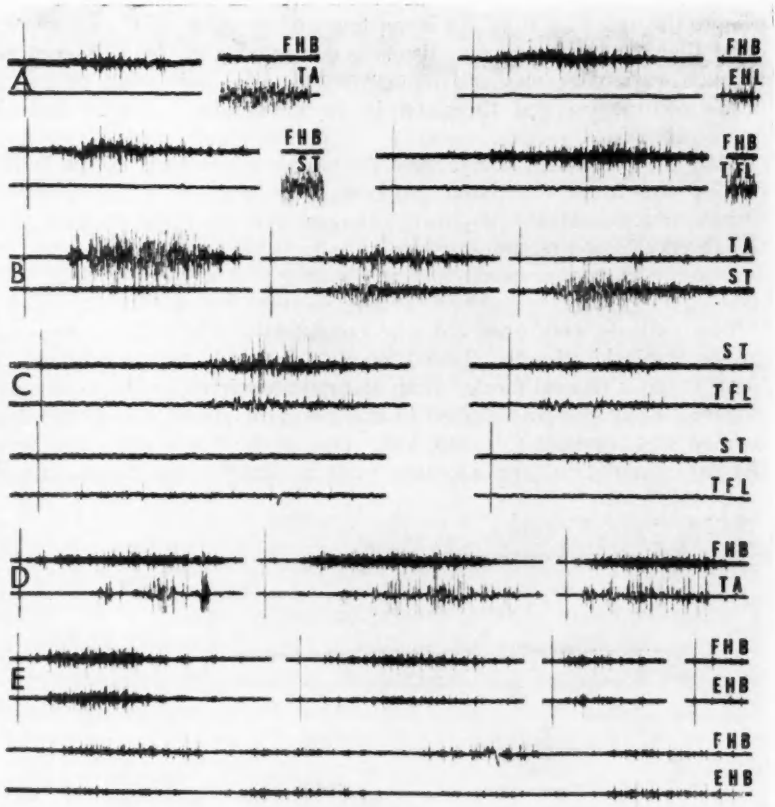

FIG. 3.—Normal plantar reflexes. A, Subject in whom the hallux flexors were the only responsive group through a wide range of stimulus intensity. Terminal segment of each strip shows muscle activation on command. B, Another subject. Variation of relative contraction intensity in tibialis anticus and semitendinosus is shown. C, Another subject. Comparison of semitendinosus and tensor fasciæ latæ thresholds. Either one may respond without the other at minimal intensities. D, Another subject. Note the variation of latency of tibialis anticus relative to the hallux flexors. E, Another subject. Upper trace shows the synchronous response in hallux flexors and extensor hallucis brevis. The lower trace shows alternate isometric flexion and extension of the hallux on command.

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In other subjects strong toe flexor responses developed without any associated responses in the leg or the thigh (fig. 3A). Variation of response pattern in the same subject was often evident. The intensity of contraction in both thigh and leg muscles might range widely, even when the stimulus and posture were kept as constant as possible (fig. 3B). Where there was a threshold difference between tensor fasciæ latæ and semitendinosus, the former was usually the lower, but there were exceptions even to this rule (fig. 3C). An inconstancy of response latency in muscles other than the toe flexors was also seen commonly (fig. 3D). In contrast to such variability was the remarkably detailed mirroring of hallux flexor contraction and threshold in its antagonist, extensor hallucis brevis (fig. 3E).

Thus the principal findings were the very low threshold of the hallux flexors, the usual associated movements in extensor hallucis brevis, tibialis anticus, extensor digitorum longus, and the thigh muscles, and the absence of contraction in extensor hallucis longus.

Transitional States

Two patients were observed who consistently gave a flexor response to the Babinski stimulus (lateral planta) and an extensor response to the Chaddock (lateral foot). Both had mild hemiparesis due to vascular disease. Only one was studied in the laboratory but the response thus defined was apparent to inspection. During the flexor reflex following plantar stimulation, the extensor hallucis longus was silent, tibialis

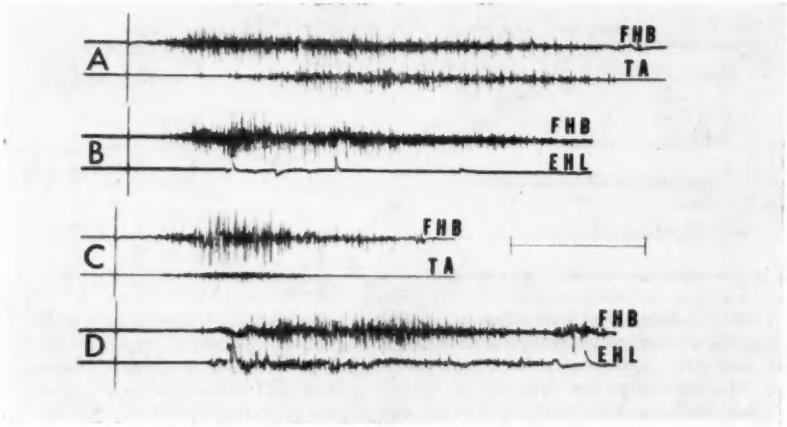

FIG. 4.—Patient with positive Chaddock and negative Babinski reflex. A, B, Plantar stimulus. Extensor hallucis longus is silent while there is vigorous response in tibialis anticus. C, D, Stimulus on the lateral foot. Extensor hallucis longus responds while tibialis anticus is relatively inactive.

anticus contracting strongly and consistently along with the great toe flexors (fig. 4A, B, fig. 5A). When the lateral surface of the foot was stroked, the result was vigorous activity in both the extensor hallucis longus and the hallux flexors; however, contraction in tibialis anticus was usually less intense (fig. 4C, D, fig. 5B). Weak stimuli in either location might elicit hallux flexor contraction alone.

This seems to demonstrate "local sign," the toe extensor being a principal target of the lateral skin area, and the tibialis anticus, of the plantar surface. Both areas effectively engage the flexors of the great toe. The finding would be consistent with the premise that tibialis anticus has

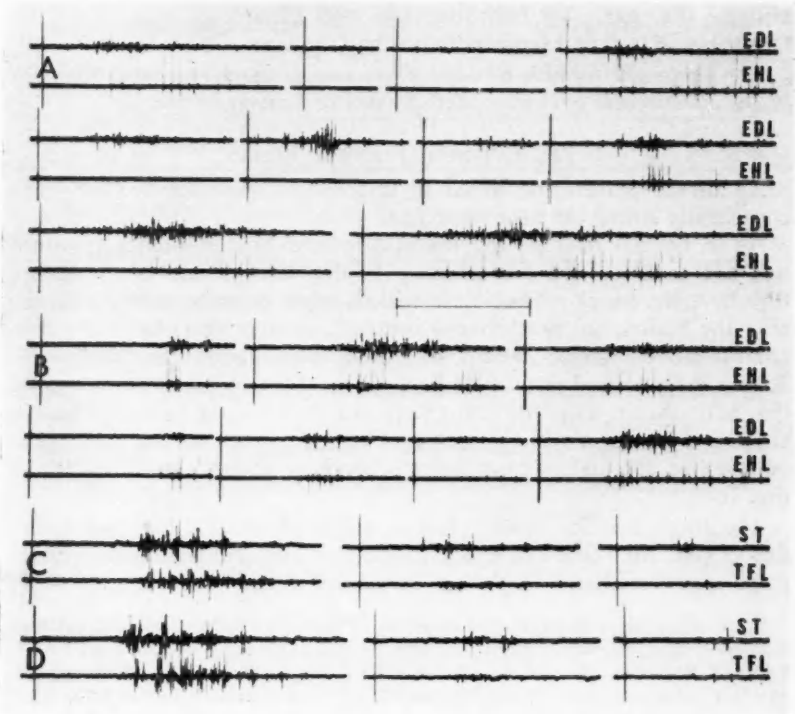

FIG. 6.—Inconstant plantar reflex. A and B are unedited records in series as elicited by minimal to moderate intensity stimuli. A, Babinski stimulus to which the clinical response was variable. Note that the relationship of extensor hallucis longus to extensor digitorum longus response is quite variable in both degree and timing. B, Chaddock stimulus, consistent extensor response. Note the good correlation of response patterns and intensities in the two muscles. C, Babinski stimulus. Similar threshold in semitendinosus and tensor fasciæ latæ. D, Chaddock stimulus. Same relative thresholds as in C.

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a more rostral segmental representation than has extensor hallucis longus, and thus responds better to a stimulus in a more cephalad dermatome.[1]

A more common condition is that where there is a variable response to apparently similar stimuli. Fig. 6 was obtained from a patient with an angioma situated in the cervical cord. The Chaddock signs were consistently extensor, while the Babinski responses, particularly to light stimulation, were sometimes flexor and sometimes extensor. With lateral foot stimulation (fig. 6B) the extensor hallucis longus consistently followed the pattern and degree of response in extensor digitorum longus. When the lateral planta was scratched, however, there was obviously a greater dissociation in timing and degree of response between the two muscles (fig. 6A). To both Babinski and Chaddock stimulation the tensor fasciæ latæ and semitendinosus had the same threshold (fig. 6C, D).

The significant variable between flexor and extensor responses seems to be the effectiveness of engagement of extensor hallucis longus.

The Extensor Plantar Reflex

All of the patients described in this section were selected for their consistently strong extensor responses.

As in normal reflexes, the lowest-threshold briefest-latency response was a 1 to 2 sec. tonic contraction in the short flexors of the hallux (fig. 7A–E, fig. 8A, B). The tibialis anticus might contract up to 300 msec. after the flexors, but synchronous contractions were also observed. The contraction of tibialis anticus was often clonic and more prolonged. Rarely it responded strongly before the peak of hallux flexor response (fig. 8C). Again, as in the flexor response, the extensor digitorum longus showed a similar threshold and contraction pattern to that of tibialis anticus (fig. 7B), and extensor hallucis brevis, to that of the hallux flexors (fig. 7C).

The thigh muscles usually had a higher threshold than the hallux flexors (fig. 7D). Though tensor fasciæ latæ and semitendinosus usually responded together, the latter occasionally had a lower threshold

[1]Most anatomical authorities, e.g. W. L. Straus, Jr. (1958), state that extensor hallucis longus, extensor digitorum longus and tibialis anticus are supplied by L4, L5, and S1 roots. Haymaker and Woodhall (1953) indicate some differences: extensor hallucis longus, L5 (slight), S1, S2; extensor digitorum longus L4 (slight), L5, S1, S2 (slight); tibialis anticus L4, L5 (slight). It is generally accepted that the short hallux flexors are supplied by segments overlapping but caudal to these extensors, i.e. L4 (slight or none), L5, S1, S2. Critical studies in the macaque where the motor roots were stimulated directly (Sherrington, 1892) showed that flexor hallucis longus like the three long extensors is supplied by sub-thoracic segments 5, 6 and 7. The short hallux flexors are innervated by subthoracic 7 and 8, and by 6 also for abductor hallucis.

In man semitendinosus is assigned innervation from L5, S1, and S2 while tensor fasciæ latæ is supplied by a higher level L4, L5 and S1.

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(fig. 7E). Its contraction typically lasted three to ten seconds longer than that of more distal muscles (fig. 8D).

The unique feature of the extensor response was the strong contraction of extensor hallucis longus (fig. 7F, G); usually this muscle also had a

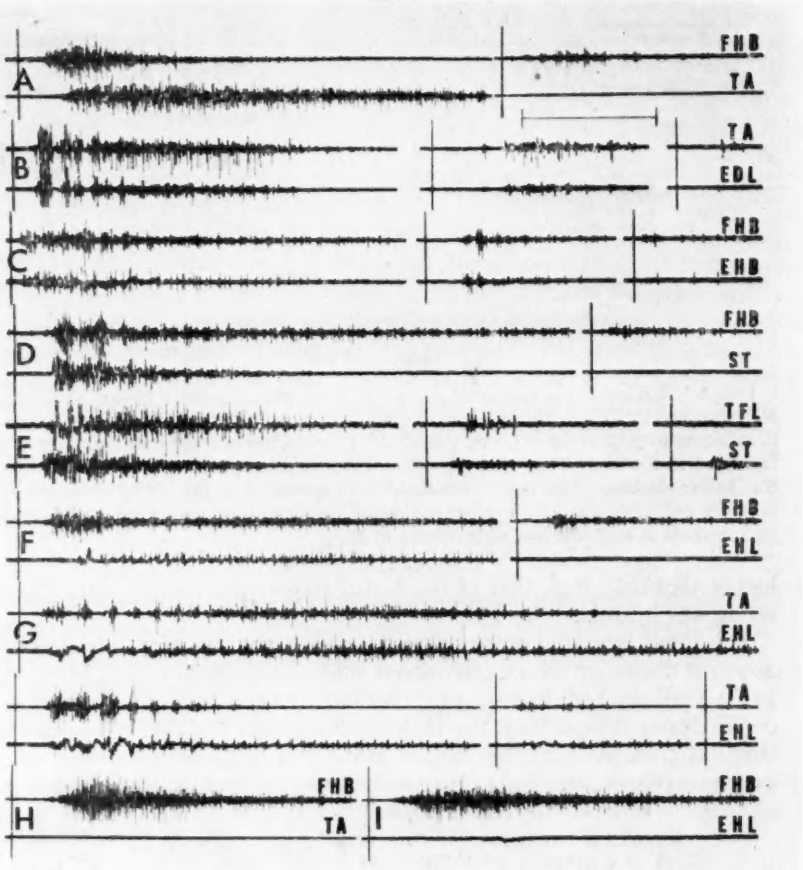

FIG. 7.—Extensor plantar reflex, unverified spinal cord lesion. A–E, Graded intensity stimuli produce response patterns indistinguishable from the normal (figs. 2, 3). F, Active response in extensor hallucis longus at higher threshold than hallux flexors. G, Similar response patterns and thresholds in tibialis anticus and extensor hallucis longus. The longer duration discharge in extensor hallucis longus is unusual. H, I, Undiminished hallux flexor response after peroneal nerve block of tibialis anticus and extensor hallucis longus. Compare with A and F.

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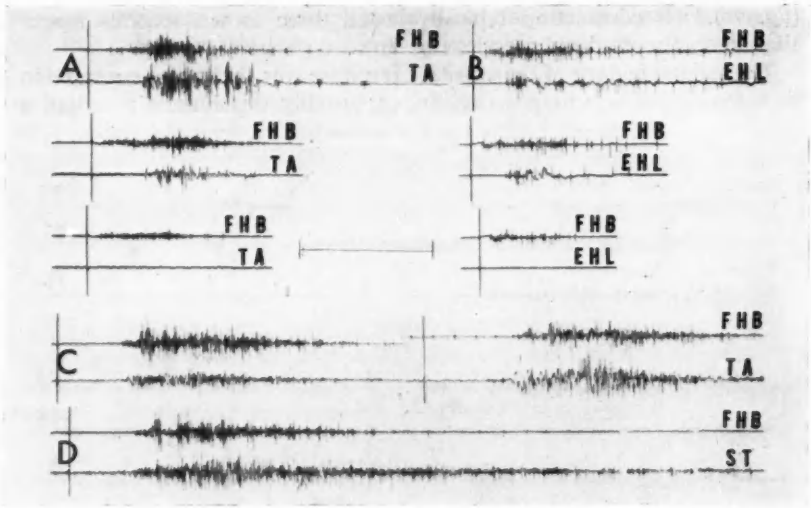

FIG. 8.—Extensor plantar reflexes. A, B, Multiple sclerosis. Lower threshold response in the hallux flexors than in tibialis anticus or extensor hallucis longus. C, D, Same subject as fig. 1H. C, Variation of tibialis anticus response intensity and latency. In the second response the initial tibialis anticus potential actually precedes the hallux flexors. The flexor threshold was nevertheless the same or lower at different examinations. D, Typical prolonged response in semitendinosus. A total of 5 seconds of response has been deleted in gaps.

higher threshold than that of the hallux flexors (fig. 7F, fig. 8B). Only rarely was it equal.

This lower threshold of the hallux flexors may be apparent to inspection as a brief flexion preceding extension (Collier, 1916; Dejerine and Mouzon, 1915; Guillain and Barrê, 1917; Walshe, 1914). In a case where we could clearly demonstrate the biphasic movement (fig. 9A, B), a weaker stimulus sometimes elicited flexion alone (fig. 9C), and a stronger one, extension alone (fig. 9D). Marshall (1954) elicited similar results by varying the intensity of electrical stimuli.

Not only was it usual for the threshold of the extensor hallucis longus to be identical with that of tibialis anticus and extensor digitorum longus (fig. 7G), but their often clonic contraction patterns were always quite similar (cf. figs. 12, 14, etc.). This dorsiflexor synergy was distinct from the usual hallux flexor and short extensor tonic pattern on the one hand, and from thigh muscle responses on the other.

The vigorous reaction we observed in the flexors of the great toe was unexpected. A ready inference would be that the tonic toe flexor response is a bracing co-contraction which is associated with a prime movement of

the toe extensors. This hypothesis was tested in 8 cases by paralysing the toe extensors with procaine block of the peroneal nerve. The contraction pattern of the flexor muscles was not significantly changed thereby (fig. 7H, I). In the first patient thus studied the response actually seemed to be enhanced. In subsequent cases stimulus intensity was controlled by using a fixed electrode attached to the skin and 100/sec. electric shocks of measured voltage. Threshold and responsiveness were not changed significantly by the block. The flexor contraction after block was, of course, palpable and it produced flexion of the toe (fig. 10). The extent of this flexion varied considerably, possibly in relation to the posture at rest.

Similar experiments were performed by Babinski (1911) using an Esmarch bandage about the leg. We made several unsuccessful attempts to produce pressure block of the peroneal nerve at the fibula by cuff compression; significant sensory loss in the foot and concomitant weakness of the toe flexors occurred before the extensors were blocked.

The essential phenomenon of the extensor reflex appears to be the recruitment of extensor hallucis longus into contraction along with the other toe and foot dorsiflexors. Whatever be the functional significance of the response of the hallux flexors, they contract as strongly in the pathological as in the normal state, and with sufficient strength when unimpeded by extensor contraction, to flex the great toe. *The development of the Babinski response therefore must be due to the mechanical overpowering of the toe flexors.*

Acute Paraplegia

The spinal shock phenomenon which occurs after cord transection offers an opportunity for the examination of the evolution of reflex patterns out of the depressed state. This development has been followed in 5 patients (Table I).

Case 1.—A 16-year-old male was thrown forward off a motorcycle. He fell prone and the motorcycle fell on his back. He was admitted to Barnes Hospital a few hours later on January 26, 1958. There was a complete sensory level at D8 and no reflexes were elicited in the lower extremities. Clinical examination on February 6 showed weak flexor responses in the great toes (fig. 11A, B), accompanied by a weak but inconstant contraction of the semitendinosus muscles. Hamstring and knee jerks were absent. The ankle-jerks were definitely present. The first EMG study was done at this time.

On February 8 the lesion was explored. The operative note (Dr. Leonard Furlow) stated: ". . . the cord was very soft and yellowish in colour. It was rotated and on its anterior surface was a laceration into the cord substance. The slightest pressure on the cord would cause necrotic cord tissue to exude through this opening. This tissue was semigelatinous in consistency and it was perfectly obvious that there had been a complete transection of the cord."

On March 7 the plantar reflexes were still flexor and there was further recovery of tendon reflexes. At the time of the final EMG examination on March 21 the right

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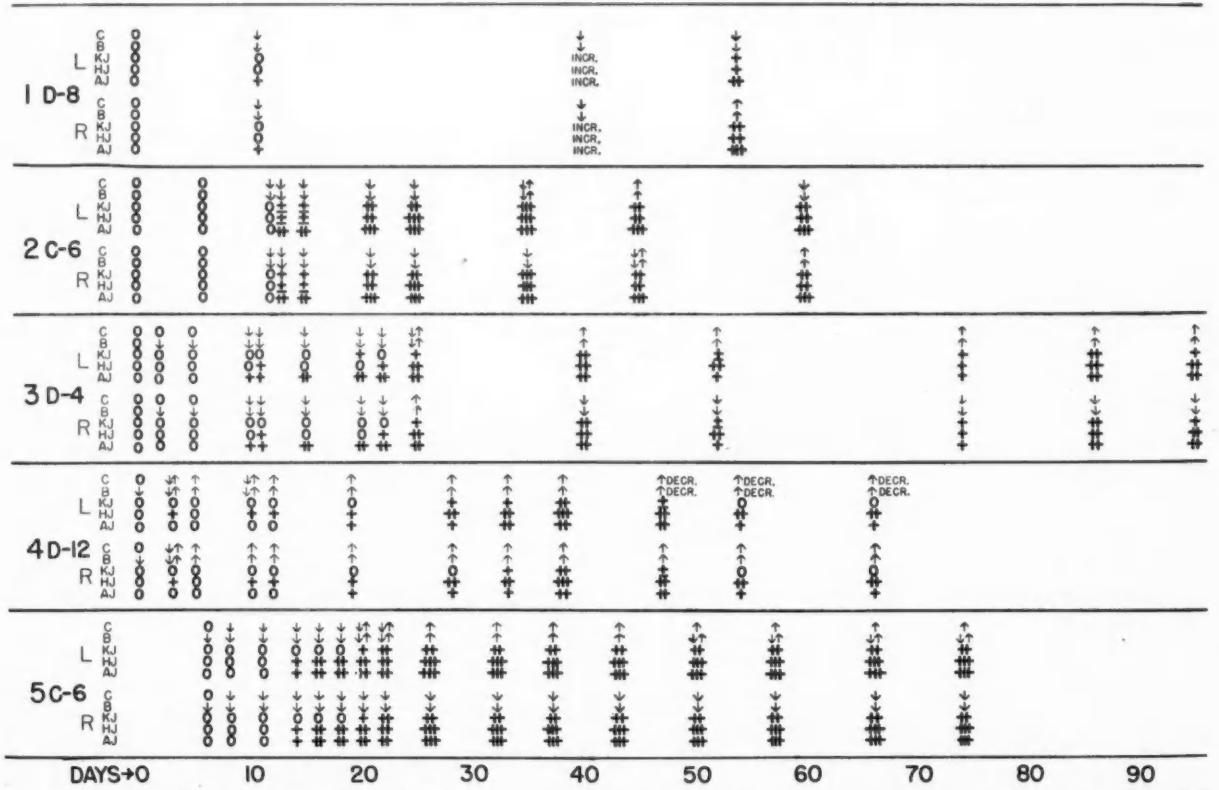
TABLE I.—REFLEX CHANGES IN THE COURSE OF ACUTE TRAUMATIC PARAPLEGIA



C—Chaddock; B—Babinski; KJ—knee-jerk; HJ—hamstring-jerk; AJ—ankle-jerk; ↑—extensor plantar reflex; ↓—flexor plantar reflex.

ankle-jerk was hyperactive with unsustained clonus, the left was 2+. The knee and hamstring jerks were brisk on the right and just perceptible on the left. Both plantar reflexes were vigorous, but hallux extension occurred only on the right (fig. 11C).

In the initial EMG, contraction of tibialis anticus and semitendinosus occurred only with maximal stimuli and then inconstantly (fig. 12A, B). No significant activity could be recorded from extensor hallucis longus. The responses were identical for both extremities.

Six weeks later the left tibialis anticus contracted vigorously and earlier, although its threshold was still higher than that of the toe flexors (fig. 12C). Semitendinosus contracted weakly at an even higher

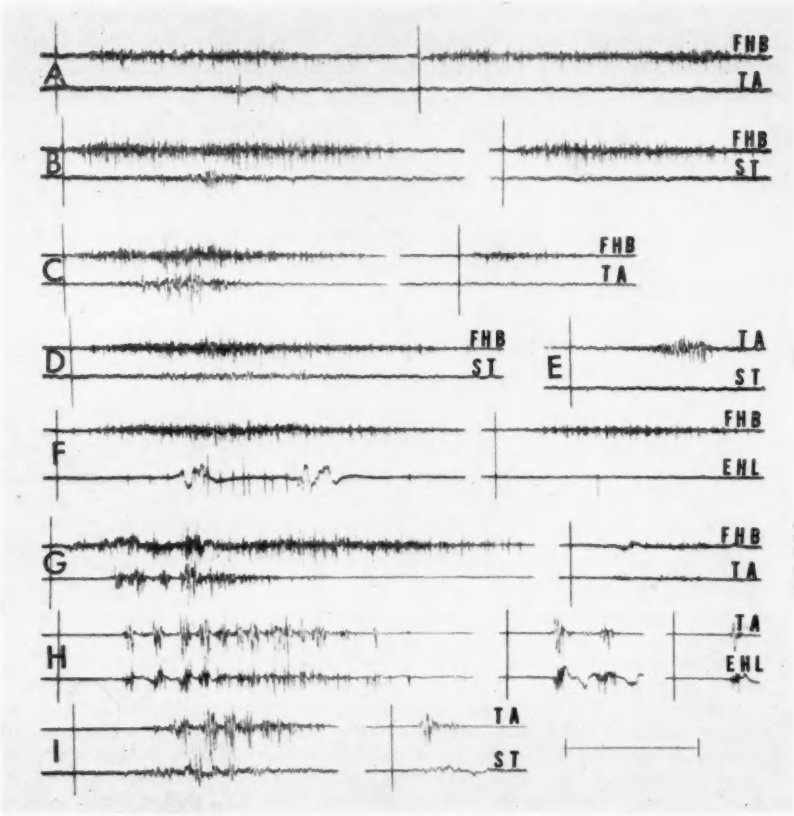


FIG. 12.—Acute paraplegia (Case 1). A, B, Left plantar reflex eleven days after accident. C–F, Same seven and a half weeks after accident. G–I, Right plantar response seven and a half weeks after lesion. Description in text.

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threshold than that of tibialis anticus (fig. 12D, E). Extensor hallucis longus now displayed fairly low threshold activity in two or three units (fig. 12F); nevertheless the great toe continued to flex.

In the right extremity both the plantar and tendon reflexes were more active. Tibialis anticus and the toe flexors had approximately the same threshold (fig. 12G), and there was also much activity of many units in extensor hallucis longus, well synchronized with the pattern of tibialis anticus (fig. 12H). The excitability of semitendinosus was also increased to approximately the same level as that of tibialis anticus (fig. 12I). No studies for evidence of denervation were performed (*vide infra*).

Thus the tendon reflexes recovered from shock in a caudo-cephalad direction, a finding compatible with the view that rostral segments suffer more intense synaptic depression because they are deprived of a larger portion of descending propriospinal tracts in addition to the loss of encephalospinal pathways. The toe flexors, innervated by more caudal segments, recovered early, the plantar reflex becoming extensor when the flexor movement was overcome by the extensor contraction. The asymmetrical recovery of reflexes showed a correlation between the evolving extensor response and the increasing activity in segmental proprioceptive reflex channels. This suggests that contraction in extensor hallucis longus is of the nature of an irradiation of the synchronous flexion response of tibialis anticus and extensor digitorum longus, both of which are usually active in the normal plantar response. It is assumed that reflex excitability had not recovered sufficiently for the development of the left extensor reflex at the time of the last examination.

Case 2.—A 15-year-old female was in an automobile accident on April 25, 1958. She sustained hyperflexion of the neck, and became immediately quadriplegic. On admission to Barnes Hospital there was a sensory level below C6 and she was areflexic. X-rays showed a compression fracture of C5 with marked posterior dislocation (fig. 13A). Crutchfield tongs were inserted and the patient was treated by traction. On May 1 she was areflexic. On May 7 toe flexion and weak hamstring contraction were noted in response to plantar stimulation. Lower extremity tendon reflexes were absent. On May 8 when the first EMG was done, the ankle-jerks were both 2+. The right knee-jerk was just perceptible. The left knee-jerk and the hamstring-jerks were considered equivocal. Plantar reflexes were both flexor and included hamstring and tibialis anticus contraction. The status had not changed on May 10. May 16 the plantar reflexes were active and flexor. The ankle-jerks were hyperactive without clonus. Both knee and hamstring jerks were 2+. On May 20 the hamstring-jerks were more active. Then on May 30 the left plantar reflex began to show an irregular extensor response. The deep tendon reflexes were slightly hyperactive, the left knee-jerk being somewhat more active than the right. On June 9 both knee and hamstring jerks were 2+. The ankle-jerks were 3+ with unsustained clonus on the left. There was an unequivocal extensor plantar reflex on the left. On the right the response was flexor, but with a quivering inconstancy similar to the May 30 observation on the left. The second EMG examination was done on June 26. Then all tendon reflexes were slightly hyperactive, the right knee-jerk being slightly more active than the left. There was a definite extensor plantar reflex on the right but flexion of the great toe was seen in the left plantar response.

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The EMG of May 8 showed vigorous tonic contraction in the right hallux flexors. (The response on the left appeared the same.) A clonic contraction of approximately equal latency and threshold was recorded from tibialis anticus (fig. 14A). There was a relatively high threshold contraction in semitendinosus (fig. 14B), and no activity in extensor hallucis longus (fig. 14C). On June 26 the EMG patterns of the right hallux flexors, tibialis anticus and semitendinosus were essentially unchanged (fig. 14D, E). However, vigorous contraction was then recorded from extensor hallucis longus synchronous with that in tibialis anticus (fig. 14F, G).

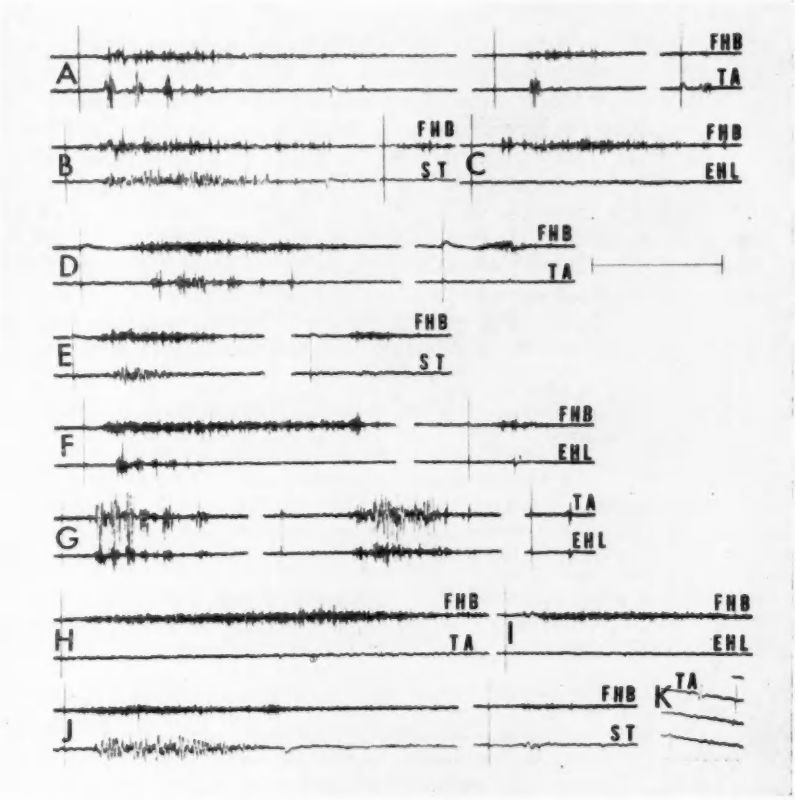

FIG. 14.—Acute paraplegia (Case 2). A–C, Right plantar reflex two weeks after lesion. D–K, Two months after lesion. D–G, Right plantar response. Note the small fibrillation spikes in extensor hallucis longus in F and G. (partly lost in reproduction) H–J, Left plantar response. K, Fibrillation potentials in left tibialis anticus. 5 msec. time base. Further description in text.

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On the left side no reflex response was noted from tibialis anticus or extensor hallucis longus. Activity in the hallux flexors and semitendinosus was similar to that on the right (fig. 14H–J).

Further study confirmed this evidence of a lower motor neuron lesion. Single shock percutaneous nerve stimulation demonstrated a good response from the musculature innervated by the left tibial nerve. Stimulation of the common peroneal nerve produced only weak contraction of peroneus longus. Tibialis anticus, extensor digitorum longus, and extensor hallucis longus were completely unresponsive. On the right side all of these muscles responded to nerve and motor point stimulation.

Fibrillation potentials and persistent sharp positive waves were recorded readily in the right extensor hallucis longus, both tibialis anticus muscles, and, with greater difficulty, in both soleus muscles. No abnormal activity was recorded from vastus medialis, rectus femoris, the adductor muscles, or semimembranosus. Thus denervation phenomena were prominent bilaterally in the peroneal innervated musculature (fig. 14F, G, K) and detectable in the tibial nerve area. We infer that the palsies were related to inadvertent pressure applied to these nerves as the patient lay supine with the extremities extended and externally rotated.

The reversal of the left extensor response is explained by the peroneal palsy. The extensor response on the right persisted in spite of a similar but less severe lesion. The general pattern of evolution of the plantar response in relation to the ascending recovery of tendon reflexes is similar to that of Case 1.

Case 3.—A 31-year-old male fell 20 feet and struck his upper back. On admission to the hospital on May 15, 1958, there was a complete sensory level at D4 and incomplete priapism. Reflexes were all absent. The operative note (Dr. William Coxe) states: "the cord appeared bluish, discoloured and quite soft. There was an almost cystic feel to it . . . contusion was approximately 2 cm. long . . . . Immediately upon passing through the pia mater an intramedullary hæmatoma was encountered which escaped through the opening. This opening was enlarged slightly and some necrotic soft cord material oozed out of the wound. This was irrigated thoroughly with saline and several sizable pieces of macerated cord were washed out. There is little question that the continuity of the cord is completely interrupted at this point, being maintained only by the meninges and perhaps some peripheral long tract ventrally."

On May 17 tendon reflexes were all absent. Plantar stimulation elicited weak left hallux flexion and just palpable great toe flexor contraction on the right. The response was unchanged on May 20. On May 25 the ankle-jerks were first observed bilaterally, and the next day, the date of the first EMG, the plantar responses were clearly flexor. There was no semitendinosus or leg muscle response. Ankle and hamstring jerks were both 1+. Knee-jerks were not elicitable. On May 30 the ankle-jerks were 2+ and the other tendon reflexes were absent. By June 4 there was a questionable left knee-jerk. On June 6 slight swelling was noted in the right knee. A few mls. of sterile fluid were aspirated. X-rays were normal. On June 9 the ankle-jerks and hamstring-jerks were both 2+. Both knee-jerks were present. The semitendinosus muscles contracted briefly in response to plantar stimulation and the

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left hallux flexed or quivered irregularly. The right hallux went weakly but consistently up. By June 26 all tendon reflexes were 2+. Now there was a flexor plantar reflex on the right and an extensor response on the left. The second EMG examination was done at this time. On July 8 the plantar reflex pattern was the same, but the ankle and knee jerks were less active. On July 14 epididymitis produced some fever which responded to treatment and on July 17 a small sacral decubitus was noted. On July 30 all the tendon reflexes were hypoactive. The plantar reflex remained extensor on the left and flexor on the right. By August 11 all tendon reflexes were reported as 2+. There was mild diffuse muscle atrophy below the knees. The plantar reflex was extensor on the left only. There was vigorous participation of the right semitendinosus in the plantar response, but no contraction of the leg musculature and only weak flexion of the hallux. These findings remained essentially unchanged through November 10. On one occasion the right semitendinosus contracted even more strongly than the left.

The EMG on May 26 showed only contraction in the left hallux flexors to stimulation of the planta. Both tibialis anticus and semitendinosus were silent (fig. 15A, B), as was extensor hallucis longus. (Both extremities responded similarly.) A month later on June 27 the left tibialis anticus did respond to plantar stimulation although at higher threshold than the hallux flexors (fig. 15C). There was contraction of semitendinosus, also at higher threshold than the hallux flexors (fig. 15D). There was vigorous activity in extensor hallucis longus, highly synchronized with that in tibialis anticus at all intensities of stimulation (fig. 15E).

On the right the response in the hallux flexors was similar to that on the left but the surface leads on tibialis anticus recorded a small amount of background activity and a single large unit which discharged according to the strength of the stimulus. The great toe flexors again had lower threshold (fig. 15F). Semitendinosus contracted vigorously as on the left but at higher threshold than the hallux flexors (fig. 15G). No reflex activity could be recorded in the extensor hallucis longus.

Electrical stimulation of the peroneal nerves elicited strong contractions on the left. On the right there was obviously weak contraction in tibialis anticus with deficient response also in extensor hallucis longus, extensor digitorum longus and the peroneal muscles. Definite fibrillation potentials were recorded from both tibialis anticus muscles and from the left extensor hallucis longus (fig. 15H, I). None were recorded in the gastroc-solei or the recti femoris.

On September 3 fibrillations and sharp waves were readily elicited from both tibialis anticus and extensor digitorum longus muscles. They were less easily recorded in both gastroc-solei. A few sharp waves were occasionally seen even in both vastus medialis muscles. The rectus femoris muscles were silent. On September 9 the paraspinal muscles were examined extensively from L1 through S1. One locus on the right opposite L4 gave rise to fibrillations. Electrical stimulation of the right peroneal nerve elicited only a weak response in peroneus longus. All

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other peroneal innervated musculature was silent to both nerve and motor point stimulation. By contrast, the posterior tibial nerve on the right and both nerves on the left gave vigorous responses.

By September 22 the degeneration on the right had progressed. Following stimulation of the planta there was only weak contraction in the hallux flexors and none in the leg muscles, though the thigh flexors were active bilaterally and the extensor response on the left was unchanged (fig. 15J, K). Fibrillation on November 10 was distributed as it had been two months before, except that no paraspinal activity was found.

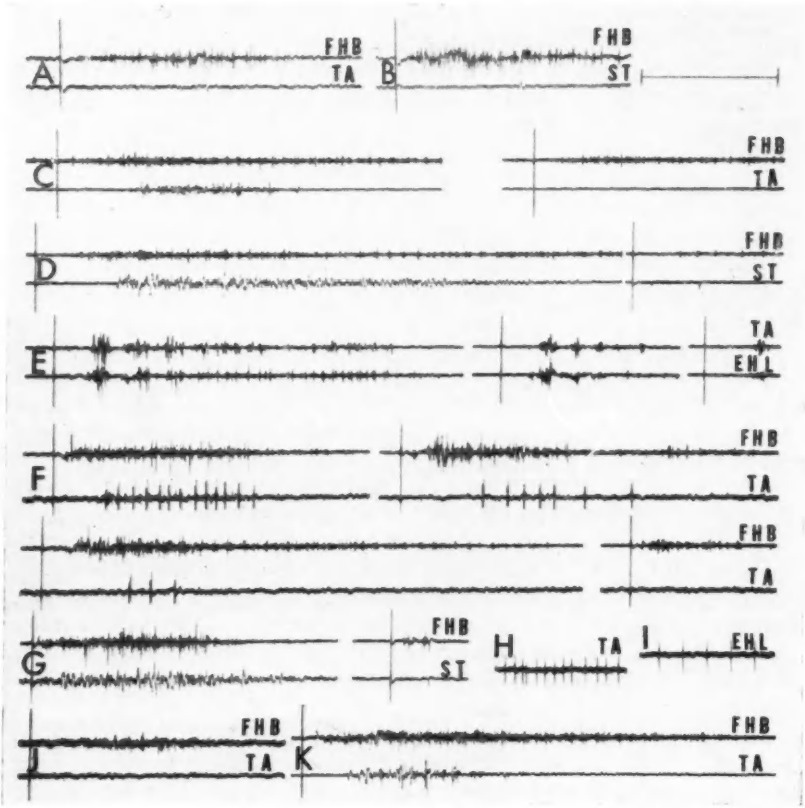

FIG. 15.—Acute paraplegia (Case 3). A, B, eleven days after lesion, left plantar reflex. C–I, Five and a half weeks after lesion. C–E, Left plantar reflex. F, G, Right plantar reflex. H, Fibrillation, right leg. I, Fibrillation, left leg. J, K, Four and a half months after lesion. J, Right plantar response. K, Left plantar response. Further description in text.

The reversal of the evolving right extensor response in this patient is again assignable to progressive peroneal palsy. Except for that contretemps, correlation with recovery of tendon reflex excitability and activity in more rostral segments of the spinal cord is similar to that seen in the previous cases. The denervation phenomena again are assignable to peripheral nerve compression. The involvement of thigh musculature, and possibly even of paraspinal muscles raises some question about this thesis. It is possible that there may be some central spinal cord "dystrophy," but it is obvious that the peroneal and tibial innervated musculature have suffered most severely.

Case 4.—A 78-year-old male fell from the roof he was repairing on September 10, 1958. He was admitted to the hospital two hours later, areflexic and showing a complete sensory level 3 in. below the umbilicus. Five hours later a flicker of plantar flexor responses was noted. Upon exploration of the lesion at D10 and D11 (Dr. Leonard Furlow) the following observations were made: ". . . a tear in the dura was exposed through which spinal cord was oozing. . . . On the left side of the cord was a penetrating wound which apparently went all the way through the cord and was about the size of a pencil. Through this, macerated cord tissue was bulging out in a mushroom fashion. . . . I am convinced that this injury is far too severe ever to permit any recovery of spinal cord function."

On September 13 plantar stimulation produced either a quivering flexor response or a twitching extension. The tibialis anticus and extensor digitorum longus usually responded, and occasionally there was also a twitch in semitendinosus. The hamstring-jerks were 1+ while ankle-jerks and knee-jerks were absent. By September 15 both plantar reflexes were clearly extensor. No tendon reflexes were elicited and no participation of semitendinosus in the plantar reflex was apparent. On September 20 only the left hamstring-jerk was perceptible of all the deep tendon reflexes. The plantar reflexes now included a twitch in semitendinosus. The right plantar was consistently extensor but on the left there was wavering and even flexion with minimal stimuli. On September 22 when the first EMG was performed, both plantar reflexes were consistently extensor with strong calf and thigh involvement (fig. 16A). The hamstring-jerks were present bilaterally. On September 29 the ankle-jerks became perceptible; there were still no knee-jerks; the plantars were briskly extensor. A second EMG was done on October 3. By October 8 weak knee-jerks were noted and the hamstring-jerks were more active. Later, on October 13, both ankle and hamstring jerks were 2+ and the knee-jerks were 1+. Plantar responses were extensor as before. The knee-jerks had increased to 2+ by October 18 but were considered equivocal on October 27. At this time (third EMG) the left extensor reflex had become obviously weaker (fig. 16B) and occasionally there was even a flexor response. On November 3 no knee-jerks could be elicited and the ankle-jerks were just perceptible. The hamstring-jerks were still 2+. The plantar reflexes were unchanged. The condition remained the same until mid-November.

The EMG examination on September 22 showed a typical extensor pattern with minimal threshold in the hallux flexors (fig. 17A, B, C). The contraction of semitendinosus had a slightly lower threshold than that of tensor fasciæ latæ (fig. 17D). Tibialis anticus, extensor digitorum longus and extensor hallucis longus had similar thresholds and contraction patterns (fig. 17E, F), and extensor hallucis brevis was similarly related to the pattern of flexor hallucis brevis (fig. 17G).

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On October 3, when there was still no clinical evidence of muscle failure, fibrillation potentials were recorded from the left extensor digitorum longus and the right tibialis anticus. The calf and thigh muscles were silent. By October 30, when a change in the left extensor response was apparent, generalized fibrillation was readily recorded from most of the musculature of the lower extremities as well as from the paraspinal muscles below the level of the lesion (fig. 17H, I). Some diffuse muscle atrophy was also becoming apparent.

This case differs from the others in that the extensor response appeared early and the hamstring-jerk before the ankle-jerk. The late recovery of the knee-jerk is similar to the finding in the other patients. The only

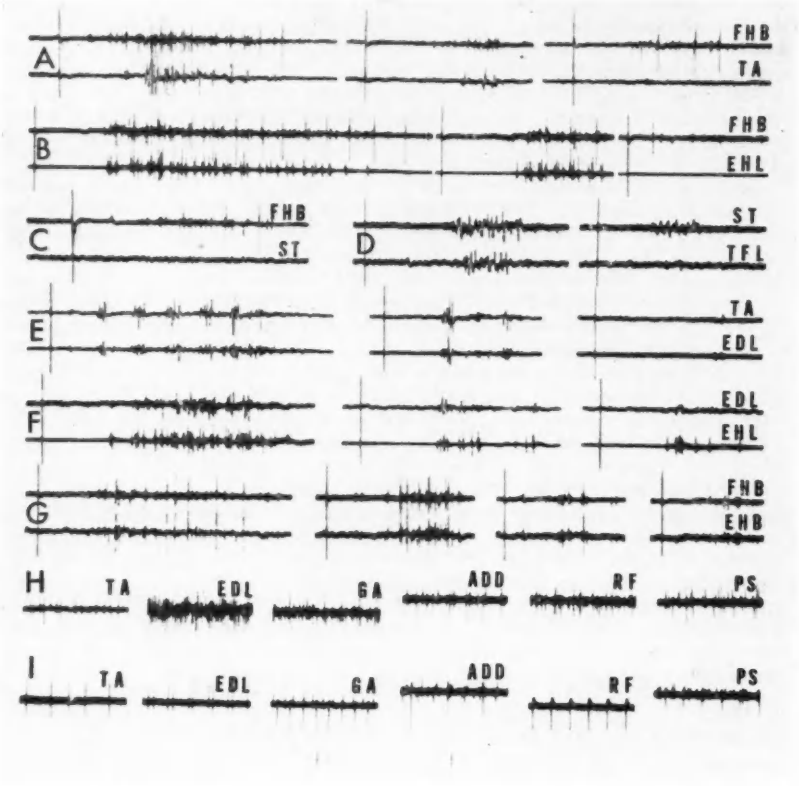

FIG. 17.—Acute paraplegia (Case 4). A–G, Typical extensor response pattern, left side, twelve days after lesion. H, I, Seven weeks after lesion, fibrillation potentials. H, Left. I, Right. Paraspinal records were taken opposite L5 and L3 spines respectively. Further description in text.

explanation we have to suggest is variation in the segmental muscle representation. In this subject the foot and hallux extensors may have recovered earlier because of a more caudal representation in the lumbosacral roots and cord. Collier (1916) also observed such early extensor reflexes following the onset of paraplegia.

The widespread denervation phenomena in this case must indicate a more diffuse lesion than compression of peripheral nerves can account for. It would not be surprising if the relatively small distal spinal cord stump in this elderly patient suffered diffuse damage due to vascular embarrassment.

Case 5.—A 21-year-old male was struck on the back of the head in a football game on November 2, 1958. He became quadriplegic immediately. The next day a laminectomy was performed at C3, 4 and the cord was reported to be irreparably compressed. He developed respiratory distress and pneumonia and was transferred to Barnes Hospital on November 8. There was a complete sensory level at C5–C6 and an X-ray demonstrated severe displacement of C4 on C5 (fig. 13B). Tracheotomy and traction with Crutchfield tongs were instituted at once and there was progressive improvement in his general condition. An additional finding was a brawny swollen contusion over the anterolateral surface of the right leg. This lesion had preceded the cervical injury by several days.

Only weak hallux flexion without leg or thigh response could be elicited by plantar stimulation on November 8. By November 10 and 13 semitendinosus responded also but the tendon reflexes were still absent. The plantar response by November 16 also included tensor fasciæ latæ; the leg muscles were silent. Ankle-jerks and hamstring-jerks were detected, but there were still no knee-jerks. By November 18 the ankle and hamstring jerks were 2+ and on November 20 tibialis anticus first participated in the plantar responses. The knee-jerks were still absent. They first appeared on November 22 and also then the left hallux began to flick upward in the plantar reflex. The right reflex remained flexor, however. On November 24 all the tendon reflexes were 2+; the left plantar was consistently extensor with strong stimuli, occasionally flexor with weak ones. On November 28 and on December 4 when the first EMG studies were done, there was no further change except that the ankle and hamstring jerks were more active and the left plantar response was consistently extensor.

On December 22 and 29 the left Chaddock response remained consistently extensor, but the Babinski response had become wavering, flexor-extensor, and when the stimulus was weak, flexor (fig. 18A, B). The right plantar response remained flexor (fig. 18C, D). Another EMG was done on December 31. There was no further change throughout January.

At the first examination in early December, electrical stimulation of the tibial nerves produced strong responses bilaterally. Left peroneal nerve and motor point responses were also normal. The responses in the right tibialis anticus and extensor digitorum longus were diminished, and there was no response in the hallux extensors at intensities several times those found to be maximal for the corresponding left-sided muscles.

Plantar stimulation elicited a relatively weaker tibialis anticus response on the right, the hallux flexors having slightly lower thresholds bilaterally. The left extensor hallucis longus had almost identical pattern and threshold

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to the tibialis anticus; the right, of course, was unresponsive. Denervation fibrillations were recorded bilaterally in the legs, most abundantly in the musculature innervated by the right peroneal nerve, but also in the left extensor digitorum longus and in both gastroc-solei. At rest, both vastus medialis and rectus femoris muscles were silent.

On December 31 the left Chaddock stimulus still consistently engaged extensor hallucis longus and tibialis anticus in similar pattern, both having the same latency as the hallux flexors. A plantar stimulus, however, elicited a strong hallux flexor response and delayed, irregular and small, or even absent reactions in both the hallux and foot dorsiflexors. Thus the hallux flexors and extensor were each more effectively engaged by stimuli in their particular dermatomal areas. The fibrillations in both legs were more prominent than previously; fibrillation was seen on one occasion in the left vastus medialis.

The ascending segmental recovery of tendon reflexes is again shown to be correlated with the reversal from flexor to extensor reflex on the left side. The old contusion of the right leg is inferred to have predisposed to the partial peroneal palsy that prevented the development of the extensor response. Again denervation is evident in both peroneal and tibial nerve distributions. It is possible that the diminished extensor potency of plantar stimuli was related to partial sensory denervation of the planta. Whatever the case, the segmental specificity of stimulus areas remains significant.

All 5 cases of acute paraplegia demonstrate that as the extensor response evolves from spinal shock, the primary contraction of the hallux flexors is overcome by extensor hallucis longus. A similar course of reflex changes occurred in 2 of Guttmann's (1952) cases, and in experimental cord transections in the monkey and baboon (Fulton and Keller, 1932).

Fulton and Keller also observed peripheral nerve degeneration in some of their animals. Peroneal palsy was seen following paraplegia in man by Guttmann, and Grossiord and Kahn (1957) pointed out that such pressure palsies can prevent the sign of Babinski.

Chronic Paraplegia without Extensor Reflexes

This phenomenon (non-extension of the hallux) occurs in a minority of long-surviving cases of complete cord transection (Kuhn, 1950; Pollock *et al.*, 1951; Boshes, 1957).

Case 6.—A 37-year-old male was in an automobile accident on October 2, 1954. He was thrown from the back seat of the car into the front one and sustained acute neck flexion. On admission there was a complete sensory level below C6 and X-rays showed severe anterior displacement of C6 on C7 vertebra (fig. 13c). Crutchfield tongs were inserted and the dislocation was reduced. At this time all reflexes were absent. On October 13, 1954, the lesion was explored and the operative note (Dr. George Hawkins) reads in part ". . . the cord was soft at C7. The vascularity was increased. It was needled in the mid-line and mushy pulped cord was aspirated.

The outlook so far as spinal cord recovery is concerned is hopeless." A note on November 15, 1954, indicates a pathological toe sign on the left but not on the right. In December 1955 there were no pathological toe signs. At this time the patient had severe decubiti over the sacrum and these were subsequently closed by plastic surgery.

At examination in 1958 he was in generally excellent condition and could move about in bed and in a chair using the residual power of his upper extremities. There was minimal generalized wasting of all extremities and prominent atrophy was apparent in the intrinsic muscles of the hands and forearms. There was good strength in both biceps, and fair strength in the triceps. The shoulder muscles were intact and minimal finger movement was evident. Pin-prick and touch were markedly diminished bilaterally over C8 segment and sensory loss was complete below that level. The biceps and radial periosteal reflexes were hyperactive bilaterally, but the triceps were absent. The abdominals and cremasterics were also absent. Hamstring-jerks were 1+, but knee-jerks and ankle-jerks were hyperactive. There was no clonus. The bladder was automatic and the patient used a condom drainage system. His skin was in excellent condition; there was no urinary infection, and no joint contractures had occurred.

Plantar stimulation on either side elicited a quivering of the great toe, a flexor tendency being disturbed by clonic extensor jerks. There was no extension of the hallux beyond the neutral position. Active contraction of the anterior calf and semitendinosus muscles was observed.

Several EMG examinations were made between February and October 1958. On the left an irregular contraction of the hallux flexors occurred in response to minimal plantar stimulation. With stronger stimulation a clonic discharge usually developed in tibialis anticus (fig. 19A). As in Case 3 (fig. 15F) surface electrodes would pick up predominantly one large motor unit from tibialis anticus in response to moderately intense stimuli. Motor unit potentials in extensor hallucis longus and extensor digitorum longus occurred synchronously with those in tibialis anticus.

The response in the toe flexors remained essentially unchanged after procaine block of the peroneal nerve. However, instead of quivering the great toe assumed a tonic flexed position (fig. 19B).

The pattern of discharge in the right limb was very similar even to the recording of a single tibialis anticus motor unit discharge at medium stimulus intensity (fig. 19C). More units were noted with maximal stimuli (fig. 19D). Activity occurred in extensor hallucis longus (fig. 19E) synchronous with that in tibialis anticus. A relatively high threshold and short duration contraction of semitendinosus was also observed (fig. 19F).

Stimulation of the peroneal and posterior tibial nerves and of the various muscle motor points revealed brisk responses in both lower extremities. Extensive exploration of limb muscles for denervation activity revealed occasional sustained fibrillations in both tibialis anticus and gastroc-soleus muscles (fig. 19G, H).

Again it appears that the absence of extensor responses is due to relative extensor weakness rather than to inadequacy of contraction pattern.

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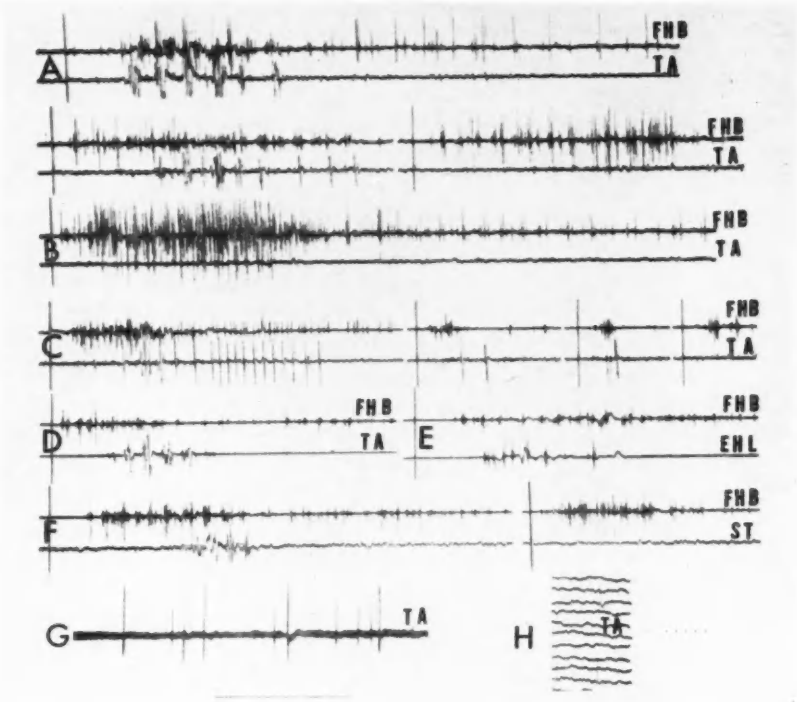

FIG. 19.—Chronic paraplegia (Case 6). A, Left plantar response showing lower threshold in the hallux flexors. B, Same as A after block of peroneal nerve. Stimulus was probably more intense. C–F, Right extremity. Record D was taken later in the examination than C, and the amplification was lower for the maximal stimulus. G, Left tibialis anticus fibrillation. H, Right tibialis anticus fibrillation. Time base 5 msec. Further description in text.

The fibrillations and the single motor unit patterns in tibialis anticus are consistent with the thesis that this case represents a late state of the peripheral nerve damage seen in acute paraplegia.

Further studies were carried out upon 7 other patients afflicted with physiologically complete chronic paraplegia due to trauma.[1] The levels of the lesions ranged from C6 to D10, and the durations since the accidents from five months to three and a half years. Ages ranged from 16 to 69 years. In 2 patients extensor responses were absent bilaterally, and in one, unilaterally. In all these severely affected

[1]We are indebted to Dr. Franz Steinberg and the Jewish Hospital of St. Louis for access to these patients.

limbs the response to peroneal and tibial nerve stimulation was decreased or absent, the latter nerves being slightly more excitable. Denervation fibrillations were clearly detectable in the affected muscles. Fibrillation was also demonstrated in the leg muscles of all the patients who had extensor plantar responses. We must conclude that significant peripheral nerve degeneration is a usual consequence of acute paraplegia in man.

Amyotrophic Lateral Sclerosis

Although most patients having this syndrome develop extensor responses at some time during the illness, observers generally have been puzzled by the number of cases showing "pyramidal" motor disability with increased tendon reflexes but without an extensor toe sign, even though the coexistent lower neuron involvement did not prevent extension of the great toe on command.

Our first case was a 72-year-old female in whom extensor plantar reflexes were present. She was still able to walk at the time of the examination and fasciculations and fibrillations (detected by the EMG)

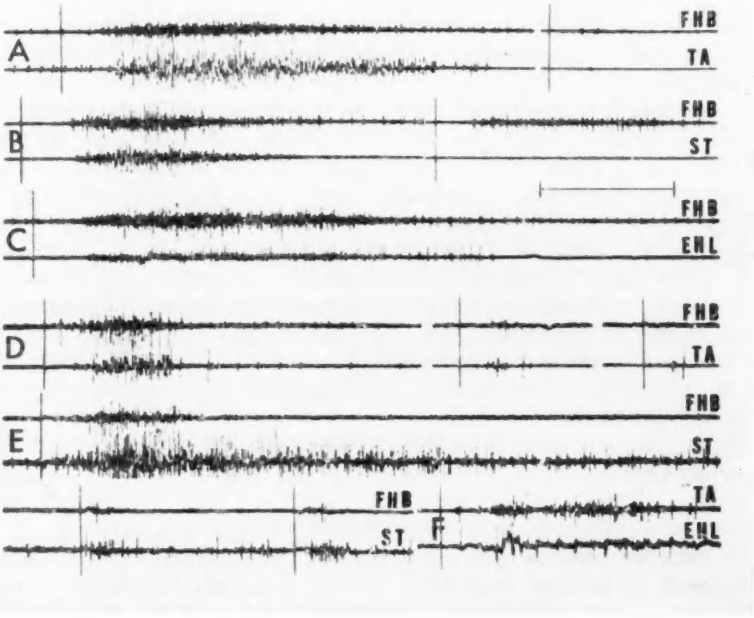

Fig. 20.—Amyotrophic lateral sclerosis. A–C, Patient with extensor response. D–F, Similar pattern in another patient with a clinical flexor response (cf. fig. 21). Further description in text.

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were generalized. Fair strength remained in all muscles of the legs and feet. The extensor reflex pattern did not differ significantly from that noted in other conditions (fig. 20A–C).

The second case was a 44-year-old female with symptoms of bulbar palsy. There were no symptoms referable to the legs, nor was any weakness detected there. Although there were generalized fasciculations, only a few fibrillations were recorded in the arms by the EMG. Both patellar and ankle jerks were hyperactive, showing unsustained clonus. The EMG of the plantar reflexes was typical of the normal flexor responses observed.

The third case was that of a 59-year-old male. He, too, showed generalized fasciculations and fibrillations (by EMG) with considerable muscle atrophy. At the time of the examination he was unable to walk without help. The right ankle-jerk was absent and the only movement noted below the knee was a trace of ankle flexion and extension in response to maximal effort. The left ankle-jerk and all other tendon reflexes were increased. On command the patient could flex and extend the left great toe, but relative weakness of toe extension was apparent. Plantar stimulation on the right elicited brisk contraction of semitendinosus with flexion at the hip and knee. A similar response occurred on the left accompanied by dorsiflexion of the foot and brisk flexion of the great toe (fig. 21).

The EMG on the left showed the usual response of hallux flexors and tibialis anticus except that here the tibialis threshold was even lower (fig. 20D). There was a prolonged response in semitendinosus, of approximately equal threshold to that of the hallux flexors (fig. 20E) and there was a consistent response in extensor hallucis longus, synchronous with tibialis anticus (fig. 20F).

Thus the EMG pattern was perfectly consistent with an extensor reflex, even though the observed response was flexor. This paradox is explicable on the ground that the extensor hallucis longus, even though reflexly innervated, was too weak from anterior horn cell decimation to overcome the hallux flexors. The degree of hallux extensor weakness may be indicated by the further observation that a few weeks after this study the patient was unable to extend the left great toe beyond the mid-position.

Discussion

The demonstration of denervation phenomena in acute paraplegia suggests re-evaluation of what has so long been considered "disuse" atrophy in that condition. We presume, of course, that fibrillation activity and nerve inexcitability do not result from disuse alone (Tower, Howe, and Bodian, 1941). The conclusion that the degeneration is due to pressure is inferential and the existence of denervation phenomena

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proximal to the knee in Cases 3 and 4 suggests that other mechanisms may also contribute.

It needs emphasis that these patients were given careful attention on the Foster frames. They were turned at two-hour intervals and none developed any skin lesions except Case 3, and that occurred after he was sitting in a chair. It is probable that such nerve compression is unavoidable unless the knee is kept partially flexed when the patient is supine. Since we became aware of this reversal phenomenon in traumatic paraplegia, it has been observed in other cases of acute paraparesis. It is presumed that some previously reported cases of transition of extensor toe signs to flexor in paraplegia (Collier, 1916) had a similar origin.

Whatever the basis for relative weakness of the extensor hallucis longus, we believe the evidence clear that it accounts for many significant variations of the release phenomenon called alternatively the extensor plantar response or the flexion reflex. Moreover, it is conceivable that motor and sensory neuron degeneration can effect changes of intraspinal synaptic mechanisms (Campbell, 1944; Downman, Eccles and McIntyre, 1953; Eccles and McIntyre, 1953).

A species of myelo-anthropomorphism has tended to confuse the operational phenomena of the plantar reflexes with their teleological justifications. Of major concern here is the normal flexor response, for Walshe's (1914) detailed study can leave no doubt of absolute homology between the extensor reflex in man and the flexion spinal reflex in experimental animals.

The view that there are *two* independent behavioural response patterns to painful stimuli, one in the normal and one in the pathological state, is *not* compatible with the experimental model. Indeed, Sherrington's essential observation was that the flexion reflex of the truncated neuraxis is a stereotyped, less variably adaptive, but remarkably accurate model of the total organism's response to a nociceptive stimulus.

The bulk of the evidence considered here indicates that the flexor and extensor responses in man are variations of a common mechanism with a common synergy. Both have specific sensory local signature in pain endings of the lateral surface of the planta and foot. In both the minimal motor response is in the flexors of the great toe. In both the organism escapes a noxious agent by bracing of the planta and by flexion at ankle, knee and hip.

The normal flexor reflex includes a wide range of response patterns: from the usually expected arched and dorsiflexed foot with stiff knee and hip, to the vigorous triple flexion of the subject approached unaware (described by Riddoch in the quotation above). Certainly the latter response is more commonly observed in everyday life when Man steps on a carpet tack or a thorn, and it seems to be more validly comparable with the response of the unconditioned spinal cord stump. Purposefully

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evading metaphysical concepts of volition and reflex, we do concur with Riddoch that the pattern of the normal plantar reflex is as much a function of the background activity of the nervous system as it is of the stimulus.

In addition to a higher degree of variability, the normal response is often characterized by more prominent contraction of tensor fasciæ latæ. These qualitative differences appear negligible compared with the similarities to the extensor response. Usually the latter is quite obviously quantitatively different, both in the greater degree of motor response, and in the gross enlargement of effective stimulus area associated with lower intensity threshold. *It is this exaggeration with irradiation, we suggest, that rather accidentally includes extensor hallucis longus in the dorsiflexor synergy of the adjacent extensor digitorum longus and tibialis anticus;* the three muscles have nearly identical thresholds and contraction patterns.

Holmes' (1915) view that the hallux flexor response is a unisegmental local response needs mention here. The striking non-correlation in many cases among the tonic innervation pattern of the hallux flexors, the clonic leg muscle jerks, and the prolonged tonic thigh muscle responses raises the possibility that there may be several spatially overlapping and interrelated response synergies. Regarding spatial localization it was clear in four of our cases that the long hallux extensor was more specifically engaged by stimuli on the lateral foot, than on the planta.

We conclude that the extensor plantar reflex is a hyperactive stereotyped form of the primary hallux flexor response, the essence of which is the recruitment of extensor hallucis longus into the higher threshold tibialis anticus-extensor digitorum longus synergy. This formulation readily justifies the demonstrated, though seemingly unorthodox mechanical opposition between toe flexors and long extensor. (Such opposition is also seen where the extensor hallucis brevis is active in the *normal* flexor plantar reflex.) The thesis is wholly consistent with the phenomena of animal physiology and, not least, it may remove some of the dogmatism, but none of the utility of the sign of Babinski. Clinical experience indicates that the long hallux extensor is not recruited into contraction within the normal range of plantar reflex response intensity.

It may well be objected that the correlation of proprioceptive reflex hyperexcitability with the extensor plantar reflex, as demonstrated particularly in the cases of acute paraplegia, is not a universal finding. The most prominent exceptions occur in two clinical circumstances where decreased tendon reflexes are associated with extensor plantar responses: cases with sensory neuropathy affecting large proprioceptive fibres predominantly, as in combined system disease, and cases of transient reflex shock following acute hemiplegia and rarely paraplegia (Case 4,

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Collier, 1916). In the former situation the proprioceptive afferent pathway is specifically interrupted. The latter observation would require the physiological explanation of depression of the monosynaptic proprioceptive reflex path at the same time that the polysynaptic flexion response becomes more active. Such a relatively pronounced depression of monosynaptic pathways in spinal shock in the monkey was observed by McCouch, Hughes and Stewart (1940). Thus we must assume not only that the summation mechanism of the internuncial neuronal pool recovers rapidly from shock, but that it becomes sufficiently potent to evoke a hyperactive flexion response, even though the reflex pathway traverses a depressed final synaptic station at the motoneurone. Such a degree of independence of mono- and plurisynaptic reflex excitability is also supported by clinical experience in some chronic cases with relatively small lesions where increased tendon reflexes and extensor plantar reflexes occur either without the other.

We do not assert that all variations from the expected extensor response are explicable by the mechanism we have proposed. Undoubtedly many other factors are important. We do wish to bring to additional attention the phenomenon which is really a summation of unknown factors; that is, individual variation. It is curious that neurologists who expect and accept such phenomena as cerebral tumors without headache or seizures, and increased intracranial pressure without papillœdema, require absolute constancy in the behaviour of the patho-physiological reflex preparation. For example, Bucy (1957), in a purposefully controversial paper, has emphasized the exceptions to some copy book maxims concerning the pyramidal tract. While his conclusion that further research is needed cannot be avoided, the need to account for exceptions is not an excuse for throwing out the rules. We may still believe that the correlation between the sign of Babinski and pyramidal tract dysfunction is a highly significant one.

Our study applies directly to the pyramidal tract controversy only in that the paraplegic cases were selected so that there can be no question that there is not gross involvement of this tract. In all of these cases peripheral nerve damage or insufficient time for recovery from shock provide an adequate explanation for those plantar reflexes which did not become or remain extensor.

In our opinion it is as absurd to deny that lesions of non-pyramidal internuncial paths may facilitate release phenomena at the spinal level, as it is to aver that the pyramidal tract is other than the most important descending internuncial pathway. In the specific context of the present work, it is usually ignored that the experimental model to which pathological responses are compared is an *inconstant* one. In a remarkably forthright paper entitled "The Rule of Reflex Response in the Limb Reflexes of the Mammal and its Exceptions," Brown and

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Sherrington (1912) emphasized the fact that many animals, both spinal and decerebrate, do deviate from the usual ipsilateral-flexion-contralateral-extension pattern.

Summary

An electromyographic analysis has been made of the human flexor and extensor plantar reflexes using normal and pathological material. Although the flexor response is characterized by some variability of muscle contraction patterns, and the extensor, by hyperexcitability and sterotypy, they share the following features in common: specific activation by pain endings and nerve fibres; minimal threshold on the lateral planta and side of the foot with high effectiveness of temporal and spatial summation; and a motor focus of contraction in the flexor muscles of the hallux, with associated flexion contractions at ankle, knee and hip.

The unique feature of the pathological extensor response is the recruitment of extensor hallucis longus into contraction with tibialis anticus and extensor digitorum longus. It is demonstrated by means of peroneal nerve block in cases with extensor reflexes, and by the study of cases of acute and chronic paraplegia and of amyotrophic lateral sclerosis, that there is an actual mechanical competition in the extensor response between the hallux flexors and extensor hallucis longus. When, for whatever local reason, the latter muscle is weak, the plantar reflex may become flexor, rather than simply absent.

It is concluded that the extensor reflex is not a different reaction from the flexor, but rather a hyperactive flexor response in which the extensor hallucis longus is included by irradiation.

An incidental finding in the cases of traumatic paraplegia is the common occurrence of peroneal and tibial nerve lesions with consequent denervation phenomena in the affected musculature.

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PLATE XXVII

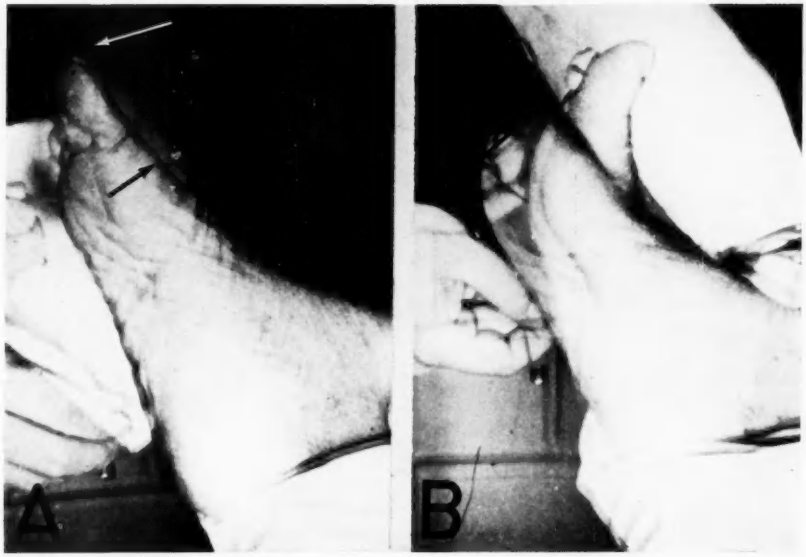

FIG. 5.—Same subject as fig. 4. Double exposure prints from movie film. A, Flexor reponse to Babinski stimulus. B, Extensor response to Chaddock stimulus.

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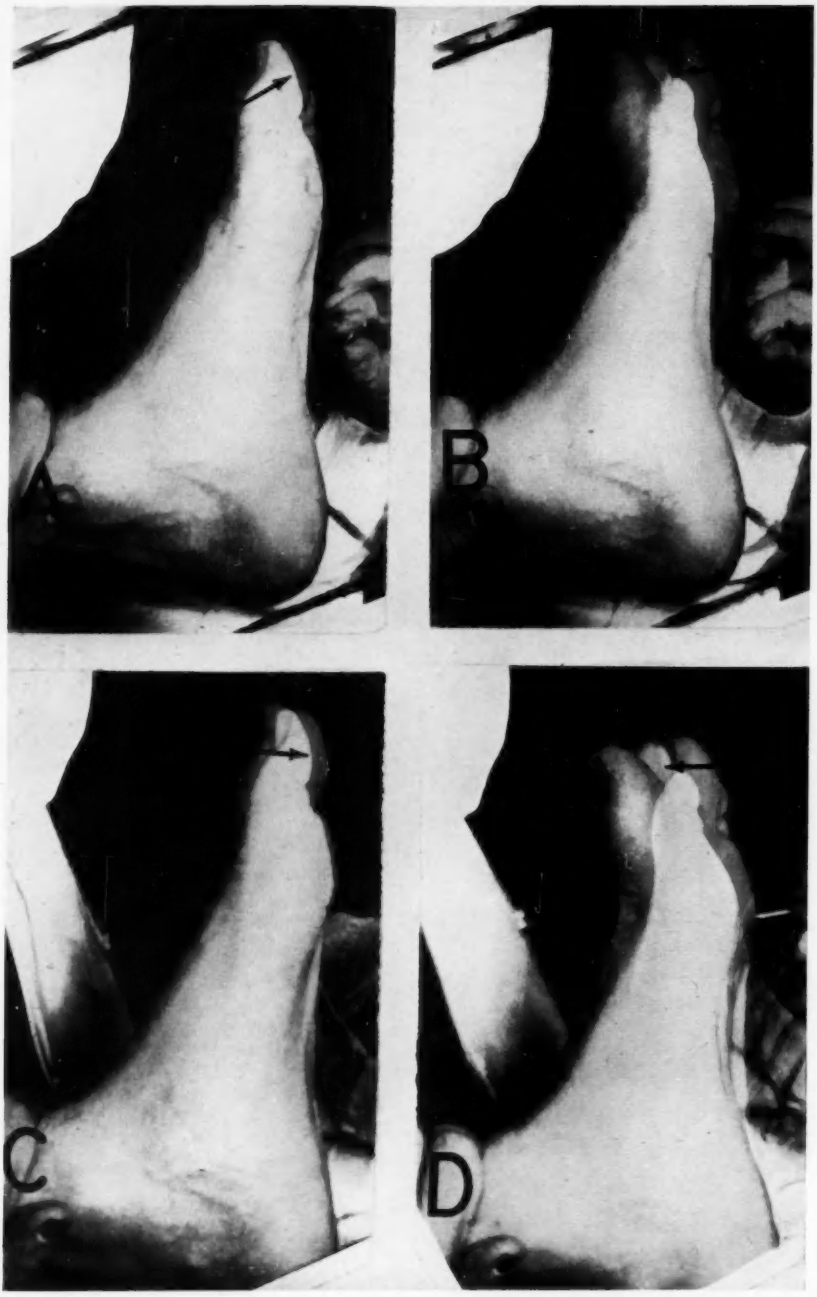

FIG. 9.—Biphasic extensor response. Traumatic paraplegia (Case 3). A, B, A biphasic reflex. A, Superposition of initial position and early flexor movement (Arrow). B, Initial position superposed with extensor terminus of reflex response. C, Minimal stimulus, plantar flexion. D, Maximal stimulus, extension without early flexion.

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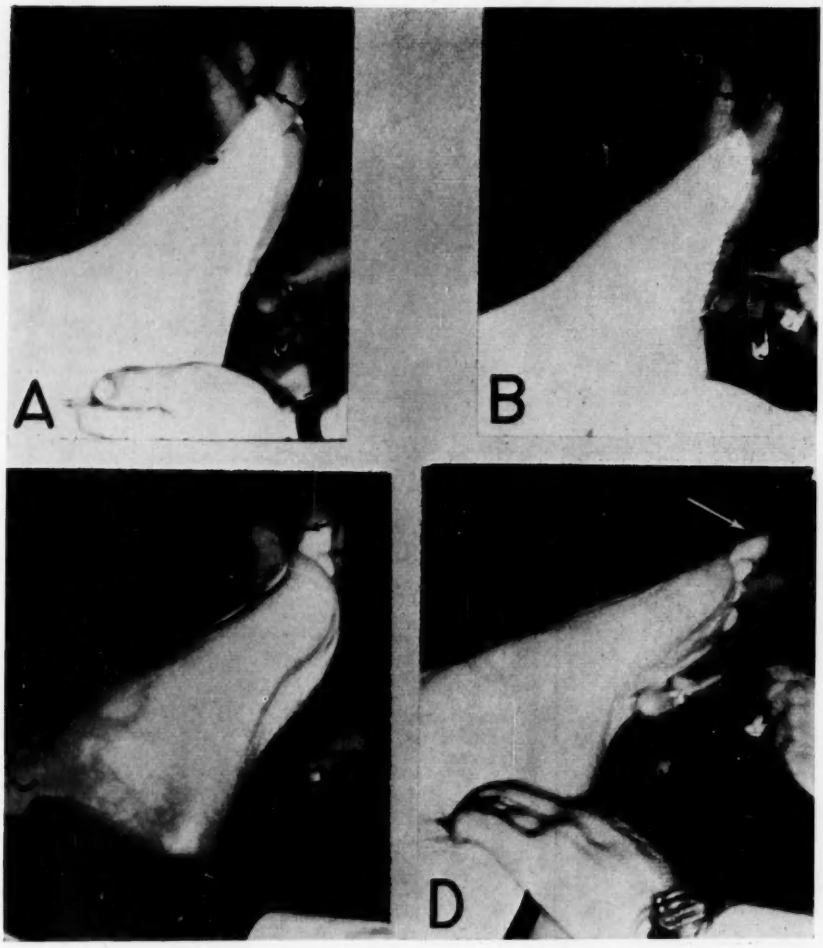

FIG. 10.—Reversal of extensor reflexes by block of peroneal nerve. A, B, Same patient as fig. 7, before and after block. C, D, Same patient as fig. 8A, B, before and after block.

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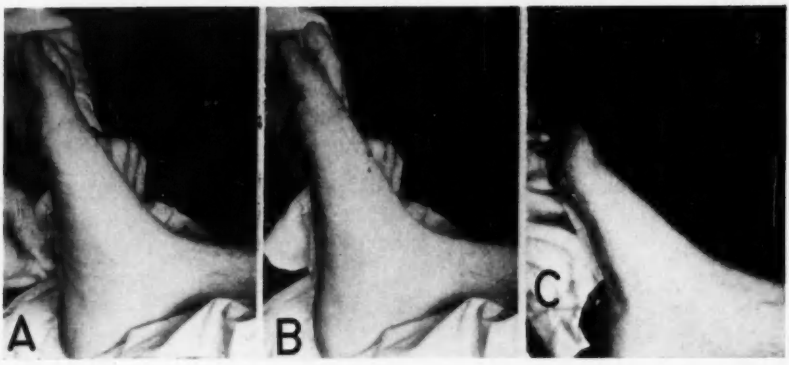

FIG. 11.—Acute paraplegia (Case 1). A, B, Serial frames to show flexor response eleven days after lesion. C, Extensor response six weeks later. Same patient as fig. 12.

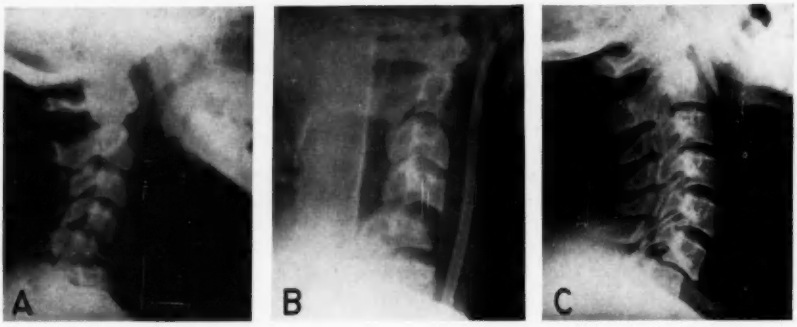

FIG. 13.—Pre-reduction X-rays of cervical spine lesions. A, Case 2. B, Case 5. C, Case 6.

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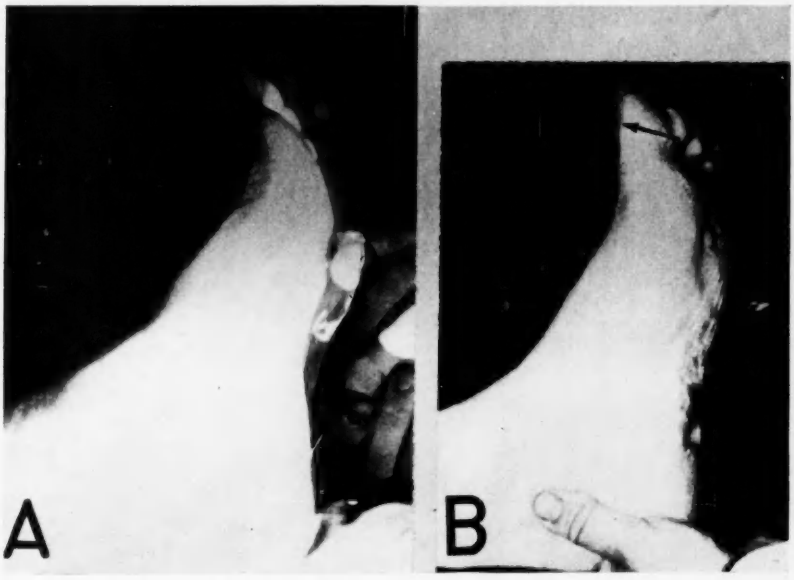

FIG. 16.—Acute paraplegia (Case 4). A, Extensor response twelve days after lesion. B, Diminished extensor response six and a half weeks after lesion. Same patient as fig. 17.

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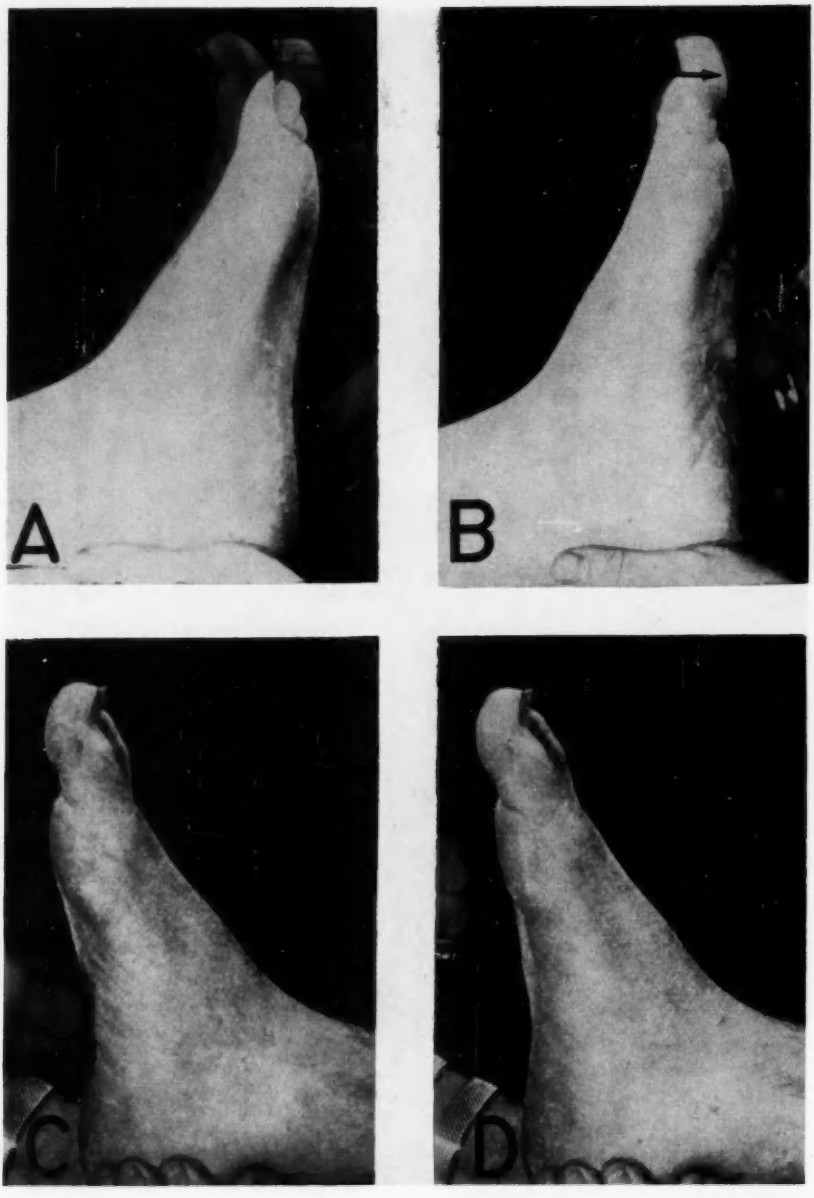

FIG. 18.—Acute paraplegia (Case 5). Eleven weeks after lesion. A, Left Chaddock response, extensor. B, Left Babinski response, weakly flexor. C and D, Serial frames to show right flexor response.

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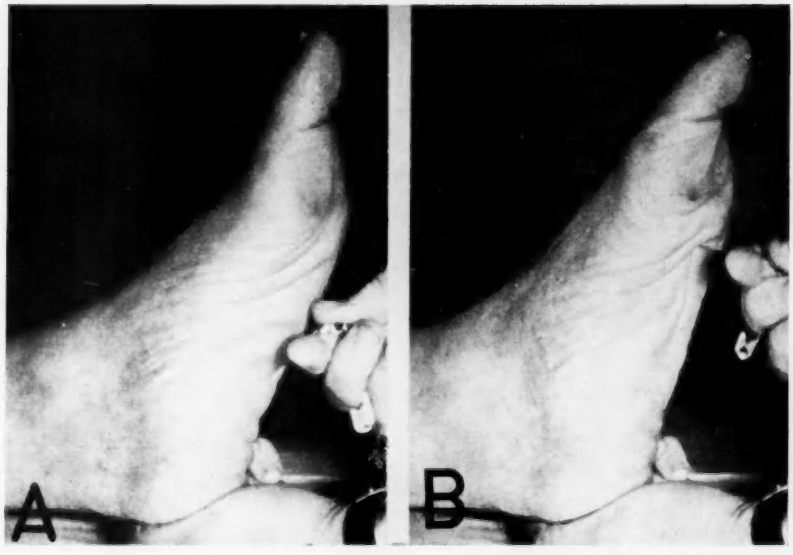

FIG. 21.—Amyotrophic lateral sclerosis. Same patient as fig. 20 D–F. A, B, Serial frames to show clinical flexor response.

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SUBARACHNOID HÆMORRHAGE

BY

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IN two earlier reports from the Neurosurgical Unit at Atkinson Morley's Hospital (McKissock and Walsh, 1956; McKissock, Paine and Walsh, 1958) the treatment of ruptured intracranial aneurysms by operation or conservative measures was evaluated but more facts were needed about the patients in associated hospitals with subarachnoid hæmorrhage who had not been transferred to our unit. Some may have died too soon and others recovered too quickly to reach us. We suspected that we were only getting those patients who had lived a few days so that our figures would be favourably weighted. At that time this delay was rarely less than two days and often one or two weeks, but today it is usually less than two days. The second report mentioned this search for those cases remaining in associated hospitals and the present paper enlarges upon the facts obtained.

Between April 1, 1954, and June 30, 1956, 408 patients with spontaneous subarachnoid hæmorrhage were admitted to our Unit from some 140 hospitals and about 200 physicians. Information was collected on other patients with subarachnoid hæmorrhage admitted to those hospitals during the twenty-seven months by a questionnaire and by personal visits. Full co-operation was given by 90 per cent of the hospitals and physicians.

As earlier reports of subarachnoid hæmorrhage excluded those patients with primary intracerebral hæmorrhage and secondary rupture into the ventricle and subarachnoid space we excluded them too and our criteria for diagnosis of primary intracerebral hæmorrhage were—an elderly patient, usually over 60 years of age with hypertension who developed a severe hemiplegia at the time of the first hæmorrhage or who immediately went into coma and died rapidly, provided a ruptured aneurysm or angioma was not found at autopsy. It is very difficult to differentiate primary cerebral hæmorrhage and hæmorrhage from a ruptured aneurysm on clinical evidence alone but it seemed important to try to do so to get a more comparable group. The subarachnoid hæmorrhage was always proven by lumbar puncture, operation or autopsy.

Using this method of selection we undoubtedly excluded some

hypertensive patients over 60 with ruptured aneurysms who died or developed severe neurological signs and thus improved our mortality figures. We probably included normotensive patients with primary intracerebral hæmorrhage who had recovered with few signs, again improving our mortality figures. This is offset by the elderly hypertensive patient with subarachnoid hæmorrhage in whom autopsy showed no intracerebral hæmorrhage but there were few autopsies on those not admitted to our Unit. There will have been patients between 40 and 60 in whom autopsy showed a primary intracerebral hæmorrhage and these will have been excluded, but not those under 40 years of age for we think the most common cause of intracerebral hæmorrhage in younger people is rupture of an angioma which disintegrates: there were very few of these cases.

In this way 373 cases were collected which, with the 408 admitted to our Unit made a total of 781 and this represents a typical group of patients with subarachnoid hæmorrhage admitted to general hospitals in the Southern part of England. No attempt was made to assess the incidence of the condition in the population at risk nor as a percentage of all hospital admissions, but that these 781 patients were admitted to hospitals associated with our Unit during a period of only two and a quarter years shows the size of the problem of subarachnoid hæmorrhage.

Pathology of Subarachnoid Hæmorrhage

Recognition of the causal lesion depends on full investigation during life or after death, lacking in many of our patients (Table I).

Table I.—Cause of Subarachnoid Hæmorrhage

Cause of hæmorrhage	*No. of patients*	*Percentage*
Ruptured intracranial aneurysm ..	355	45
Ruptured intracranial angioma ..	36	5
Unexplained	390	50
Total	781	100

Intracranial aneurysms were demonstrated by angiography, operation or autopsy in 355 patients, their sites being shown in Table II. Angiomas

Table II.—Site of Ruptured Intracranial Aneurysm

	No.	*Percentage*
Anterior cerebral—Anterior communicating	102	31
Internal carotid—Posterior communicating	70	21
Middle cerebral artery	60	18
Bifurcation of internal carotid	26	8
Vertebral system	15	5
Peripheral anterior cerebral artery	8	2
Multiple	49	15
Site not specified	25	—
Total	355	100

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were shown in 36 patients but in the remainder the causal lesion was not known. Some had an autopsy which showed subarachnoid blood and the absence of intracerebral hæmorrhage but not the anomalous ruptured vessel: many died without autopsy and many were alive having had no investigation beyond a lumbar puncture to confirm the diagnosis of subarachnoid bleeding.

Four patients had aneurysms and 8 angiomas of the 26 under the age of 20 years. Sixty-four aneurysms and 12 angiomas were found in the 127 between 20 and 40 years of age but 287 aneurysms and 8 angiomas in the 628 who were older than this. Rupture of an intracranial aneurysm was thus the most common cause of spontaneous subarachnoid hæmorrhage after the age of 20 years. The proportion of unexplained cases increased with rising age, presumably due to the desire not to investigate the older patients with an intracranial vascular catastrophe.

Investigation

Angiography, autopsy and operation are the only investigations which will demonstrate the causal lesion in subarachnoid hæmorrhage. Unilateral or bilateral carotid angiography was performed in 429 patients and a few also had a vertebral angiogram. The angiogram showed the causal lesion in 278 instances (65 per cent).

Operation, except for evacuation of an hæmatoma, was not undertaken without a positive angiogram so there were very few cases where the diagnosis had been made at operation alone.

Autopsy was performed in 237 patients demonstrating the aneurysms in 178 and angiomas in 17. In the other 42 the presence of subarachnoid blood and the absence of intracerebral hæmorrhage was confirmed but no aneurysm or angioma was shown. In 6 of these the hæmorrhage appeared to come from a particular vessel and it is likely that an aneurysm or angioma had disintegrated on rupture but in the others even the vessel at the site of origin was not determined.

Sex and Age Incidence (Table III)

There were 304 males and 477 females, a proportion on 1 : 1·57 of approximately 2 : 3.

Table III.—Sex and Age Grouping of 781 Patients with Subarachnoid Hæmorrhage

	Age Groups									
Sex	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	*Total*
Male	0	17	24	37	71	94	49	10	2	304
Female	2	7	24	42	116	132	106	43	5	477
Total	2	24	48	79	187	226	155	53	7	781

The maximum age incidence was between 40 and 70 years and 73 per cent came within this age group. The mean age of the males was 50

years and of the females 53 years with a mean of 52 for the whole group. Fig. 1 shows this age and sex incidence graphically and illustrates that the

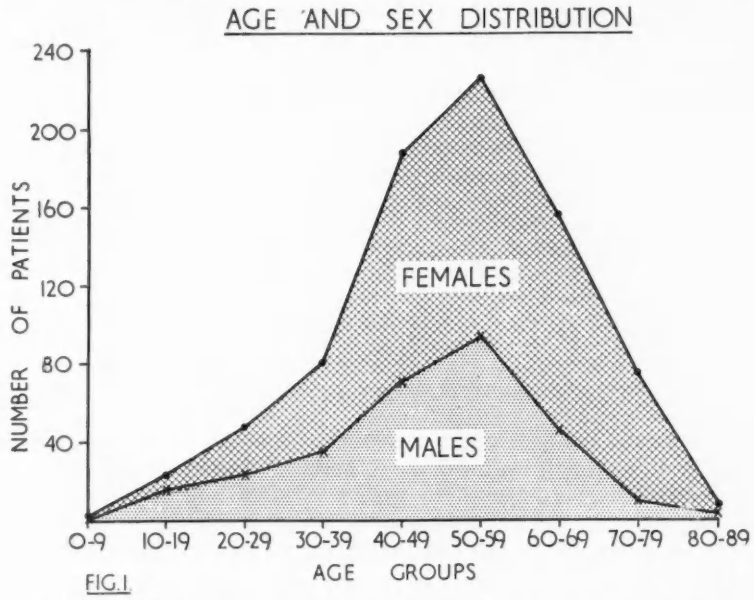

FIG.1

sex ratio remains the same in each decade. Children were not usually admitted to the Neurosurgical Unit and thus the number of patients under the age of 15 years was lower than might be expected but this is not an important factor for the incidence of the condition in children was less than 1 per cent of over 1,000 cases of subarachnoid hæmorrhage admitted to one of two adult and one children's neurosurgical units (recent personal observation). The incidence of aneurysms in the different decades coincides closely with that of the unexplained cases and there is the same preponderance of females (3·2). The mean age of males with aneurysms was 51 years and females 53 years with a mean of 52 years for both sexes.

The smaller number of patients with angiomas does not greatly influence the group as a whole but the mean age of these patients was 37 years and this is in accord with previous reports.

Blood Pressure

Forty-three per cent of patients were normotensive, with a blood pressure below 160/90. The distribution of the patients in relation to blood pressure was identical in the patients with proven aneurysms as in the remainder of the group.

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Recurrent Subarachnoid Hæmorrhage

Five hundred of our patients had one bleed only (65 per cent). One hundred and ninety eight (26 per cent) had two bleeds, 59 had three and 16 more than three subarachnoid hæmorrhages. We had insufficient information about the other 8 patients (Table IV). Thus 273 patients had more than one subarachnoid hæmorrhage (35 per cent).

Table IV.—Recurrent Subarachnoid Hæmorrhage

No. of bleeds	*Patients with aneurysms*		*Patients without aneurysms*		*Total*	
	No.	*Percentage*	*No.*	*Percentage*	*No.*	*Percentage*
One	199	57	301	71	500	65
Two	104	29	94	22	198	26
Three	41	12	18	4	59	8
Four or more	7	2	9	2	16	2
Total	351		422		773	

Adequate information was not available in 8 patients.

These figures bear no relation to the natural course of the disease as operation was performed in a large number of cases after the first or any recurrent hæmorrhage.

Interval Between First and Second Hæmorrhage

Table V shows the interval between first and second hæmorrhage and it is noted that in 41 per cent this interval was less than one week and in

Table V.—Interval Between First and Second Hæmorrhage

	Causal Lesion			
	Aneurysms	*Angioma*	*Unexplained*	*Total*
Less than 1 day	5	0	6	11
1–2 days	8	0	11	19
2–3 days	6	2	8	16
3–4 days	9	0	4	13
4–5 days	12	0	7	19
5–6 days	10	0	5	15
6–7 days	15	0	4	19
Less than 1 week	65	2	45	112
1–2 weeks	29	1	15	45
2–8 weeks	40	0	23	63
More than 8 weeks	18	10	25	53

57 per cent was less than two weeks. This interval was the same whether the causal lesion was an aneurysm or had not been demonstrated. In patients with angiomas, however, the interval was less than two weeks in only 3 of 13 cases and in the remaining 10 was more than eight weeks.

Results of Treatment

The majority of the patients were treated conservatively, details of the regime differing from hospital to hospital but based on a period of absolute bed rest for from four to six weeks and then gradual mobilization. Approximately one-quarter of the group were operated upon. Morbidity figures were not suitable for detailed analysis as the follow-up was not good except in the operated patients. Similarly any mortality figures must allow for the fact that many patients treated conservatively had not been seen since discharge from hospital.

Table VI shows the mortality in the whole group and of the patients

Table VI.—Mortality in 781 Cases of Subarachnoid Hæmorrhage

Causal lesion	*No. of patients*	*Deaths*	
		No.	*Percentage*
Ruptured aneurysm ..	355	203	57
Ruptured angioma ..	36	14	39
Unexplained	390	141	36
Totals	781	358	46

with aneurysms or angiomas. The mortality of those patients with angiomas and aneurysms is high as it includes those in whom the diagnosis has been made at autopsy and the deaths in the unexplained group include 99 in whom no autopsy was done. The mortality of the whole group was 46 per cent and includes all deaths irrespective of time. 38 per cent of the 204 operated patients died and 49 per cent of the 577 treated conservatively.

Table VII shows the length of follow-up of the survivors and indicates

Table VII.—Length of Follow up in Survivors

	No.	*Percentage*
Less than 1 month	86	20
1–6 months	69	16
6–12 months	93	22
1–2 years	110	26
2–3 years	57	13
3–4 years	8	2
Total	423	100

that more than 20 per cent were not seen after discharge from hospital, and Table VIII shows the high proportion of deaths in the first month. Combining these figures we obtain the prognosis of the patient who has survived a specific time since his hæmorrhage (Table IX).

An estimate of the mortality if adequate follow-up were available could be made by calculation assuming that the known mortality of

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TABLE VIII.—TIME OF DEATH AFTER HÆMORRHAGE

	Neurosurgical unit	*Outside hospitals*	*Total*	*Percentage*
Within 24 hours ..	7	63	70	19·5
1–7 days	28	77	105	29·4
7–14 days	33	33	66	18·5
2–4 weeks	26	37	63	17·5
1–6 months	37	2	39	11
More than 6 months	8	7	15	4·1
Total deaths	139	219	358	100
Total No. of patients	408	373	781	
Mortality percentage	34	59	46	

TABLE IX.—PROGNOSIS IN RELATION TO TIME AFTER HÆMORRHAGE

Time after hæmorrhage	*Surviving patients*	*Died at some time later*	
		No.	*Percentage*
One day	711	288	40
One week ..	606	183	30
Two weeks ..	540	117	22
Four weeks ..	477	54	11
Six months ..	438	15	3

those followed for a particular period was the same as in those not followed up. Thus, 394 patients were actually followed for from one to two months and during this time 23 of them died (6 per cent). However, 480 were known to have survived one month so that one might expect 29 of them to have died by the end of the second month. Calculated in this way, the estimate for corrected mortality over a period of four years was 400 or 51 per cent.

The mortality was shown to be influenced by various factors—it rose with increasing age (Table X)—it was higher in the hypertensive patients—

TABLE X.—PERCENTAGE MORTALITY IN RELATION TO AGE

Age in years ..	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89
Percentage mortality	50	21	35	41	36	49	57	57	71

51 per cent compared with 34 per cent, and it was higher with recurrent hæmorrhages—24 per cent after a first hæmorrhage—42 per cent after a second hæmorrhage and 61 per cent after a third bleed. The operation mortality after the first hæmorrhage was 31 per cent, after the second 49 per cent and after the third was 38 per cent.

If we considered that the aim of surgery in most operations on aneurysms was to prevent further hæmorrhage, some interesting facts emerge: 22 per cent of patients died as a result of their first bleed and

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probably would not have been helped by surgery, so that 26 per cent died later from a recurrent hæmorrhage which might have been prevented by operation. Twenty-five per cent of patients surviving a second hæmorrhage died from a later bleed and similarly 28 per cent who survived a third bleed died from a later hæmorrhage. Thus following survival from any subarachnoid hæmorrhage the patient has about a one in four chance of dying from a later bleed.

That selection of patients for transfer to the Neurosurgical Unit occurred is indicated in Table VIII which shows that 29 per cent of the deaths in the associated hospitals occurred within twenty-four hours of the hæmorrhage whereas only 5 per cent of those admitted to the Neurosurgical Unit died within this time.

Discussion

Subarachnoid hæmorrhage as an entity has been replaced by the more accurate diagnoses of ruptured intracranial aneurysm, or ruptured intracranial angioma although still leaving about one-third of the cases unexplained. Reports are of greater value if the cause of the subarachnoid hæmorrhage is known and for surgical treatment this is essential. A report of a group of patients with subarachnoid hæmorrhage may still be of some value if a sufficient number have been adequately investigated to draw deductions on the frequency of each causal lesion and so that comparisons can be made with other reported series. The main advances in treatment will only be seen when the more limited diagnosis of ruptured aneurysm or angioma are considered separately.

This present series of patients was collected from a catchment area of some 140 hospitals which drain into the Neurosurgical Unit at Atkinson Morley's Hospital and included as far as possible all cases of proven spontaneous subarachnoid hæmorrhage. The method of elimination of patients with primary intracerebral hæmorrhage has been mentioned though some of these may have been included in our series. This just confirmed that the diagnosis of subarachnoid hæmorrhage is too loose to be of much value.

Our reason for presenting this paper is to compare our patients with those of previously reported series to determine whether surgery, practised in a quarter of our patients, has had any obvious influence on the outcome of the group as a whole. In the series with which comparisons are to be made surgery was applied to very few patients.

The commonest cause of spontaneous subarachnoid hæmorrhage is rupture of an intracranial aneurysm and in our cases this accounted for 45 per cent of the patients, a much lower proportion than in the series of Taylor and Whitfield (1936) Richardson and Hyland (1941), Magee (1943) and Walton (1956). In these series, however, we find that the frequency of aneurysms has been calculated on the number of autopsies,

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a small proportion of the total cases. If we calculated the incidence of proven aneurysms in those patients who had had the lesion demonstrated by autopsy we find an incidence of 75 per cent, an incidence almost identical with these previous reports.

Intracranial angiomas accounted for about 5 per cent of our cases and this is higher than in earlier series but as Walton says, the incidence of intracranial angioma as a cause of subarachnoid hæmorrhage will be higher in a group of patients than when studying autopsies since a rupture of an angioma is less fatal than that of an aneurysm.

In 2 patients the subarachnoid hæmorrhage may have been associated with a bleeding diathesis but approximately half the cases were unexplained.

Investigation by angiography was the first step in localization of the causal lesion but for our comparisons angiographic diagnosis cannot be used, since only 10 of Walton's patients and none of those of the other series mentioned had had angiograms performed. It is our experience that two-thirds of the angiograms in patients who have had a subarachnoid hæmorrhage will show aneurysms or angiomas.

Study of autopsy material cannot give a true picture of the natural history of ruptured intracranial aneurysms unless autopsy is obtained in every patient admitted with a subarachnoid hæmorrhage, many of whom may survive many years. The sex and age incidence of our patients agrees with the earlier reports although a preponderance of females is not universal. The mean age of our patients is higher than those of Richardson and Hyland and of Walton but it is probable that this present series is more representative of patients admitted to general hospitals in respect of both age and sex. One very interesting feature emerges from our own series and that is the parallel between the patients with aneurysms and those in whom the cause of the subarachnoid hæmorrhage is unexplained. The sex incidence is the same in the two groups and the age incidence is roughly the same. Although this latter finding could be due to our method of rejection of cases with intracerebral hæmorrhage, this could not be said of the former. There is thus some suggestion that the majority—about 90 per cent—of cases of subarachnoid hæmorrhage are due to a ruptured aneurysm.

Recurrent hæmorrhage occurred in 35 per cent of our cases and this is roughly in agreement with the rates quoted by Walton as varying from 19 per cent to 47 per cent. We also noted that recurrent hæmorrhage was more likely in patients with proven intracranial aneurysms but this may be merely a reflection of the insufficient investigation of a patient who has survived his only hæmorrhage.

Thirty-five per cent of Walton's patients were hypertensive compared with more than half of ours, but his level of normal was set slightly

higher than our own. It seems that we are more nearly in agreement than the figures would suggest.

It is apparent that this present series, although broadly comparable with the series of Richardson and Hyland, Taylor and Whitfield and Walton, does differ slightly but nevertheless we must compare it with these previous reports as far as the results are concerned.

The mortality of the patients in our series was 46 per cent although we have calculated an expected mortality over a four-year period as about 51 per cent. If we further corrected our mortality to allow for those hospitals and physicians from whom we were unable to obtain details of other cases of subarachnoid hæmorrhage, our mortality would be only about 1 per cent higher.

This compares with 63·4 per cent of the patients of Taylor and Whitfield, 52 per cent of Richardson and Hyland and 56 per cent of Walton's series, so that our mortality is slightly lower but not significantly so. Walton also tabulates the mortality rate reported by a number of different authors for hospital deaths (deaths within two months) and gives an average of 45 per cent for a total of 1,480 patients. The mortality rate of our patients at the end of two months or at discharge from hospital was 41 per cent again slightly lower but not significantly so in view of the wide range quoted by Walton ranging from 28 to 63 per cent.

We have no indication on these gross figures to show that operation performed upon 204 of our patients has significantly lowered the mortality of the group as a whole.

The time of death agrees roughly with that given by Walton as does the chance of survival at a specified time after the hæmorrhage. The benignity of the angiomas is brought out. The hypertensive fare less well than the normotensive and this again is in agreement with other series. We have also shown that the mortality increases with rising age although in our cases this does not become a factor of significance until after the age of 60 years. This again is a finding previously reported although not universally. It is significant that a considerably higher proportion of the deaths occurring in the associated hospitals were in the first twenty-four hours, showing that one of the prerequisites for transfer to a Neurosurgeon was ability to survive the immediate effect of the hæmorrhage.

Summary

Seven hundred and eighty-one patients with subarachnoid hæmorrhage are compared with series previously reported in the literature. It is shown that these groups are similar as regards age, sex, proportion of hypertensives and proportion of aneurysms found but about one-quarter of the present series had been operated upon. When comparing the mortality of our own patients and those of

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previous reports in the literature we found that there was no significant difference which might be attributed to the surgery offered to a large number of our patients. Presumably the low surgical mortality was obtained in a group of patients who survived long enough to reach a Neurosurgeon and in whom the prognosis was better than in a truly representative group of patients who had sustained a subarachnoid hæmorrhage.

We conclude that because of the difficulty of clinical diagnosis in this group of patients—diagnosis of the causal lesion—no proof of the value of surgery can come from a study of a large group of patients whose only common factor is the presence of blood in the cerebrospinal fluid.

We wish to thank Mr. Valentine Logue for permission to use records of patients who were under his care and also the many physicians of associated hospitals who were so helpful in allowing access to their records of patients with subarachnoid hæmorrhage.

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REDISTRIBUTION OF BLOOD TO THE BRAIN DUE TO LOCALIZED CEREBRAL ARTERIAL SPASM

THE POSSIBLE IMPORTANCE OF THE SMALL PERIPHERAL ANASTOMOTIC CEREBRAL ARTERIES

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The Importance of Arterial Diameter

The greatest single factor influencing the volumetric rate of flow of a liquid is the *fourth power of the diameter of the tube* through which it passes. It is still uncertain how strictly this part of Poiseuille's law is applicable to blood in an artery, but the factor is something of this order of magnitude and the D^4 law will be assumed for the purpose of the calculations that follow.

If the diameter of an artery is much narrowed, an enormous increase in the *pressure gradient* along its length will be necessary to maintain the original flow, for the relationship between pressure and flow is a simple one. Similarly, a drastic reduction in the *viscosity* of the blood or in the *length* of the artery (were this feasible) might go some way to producing the desired compensation; but in practice it seems impossible that any of these mechanisms can be of much importance in an arterial system—blood that is owing to a jeopardized organ will go, whenever it can, through alternative channels, anastomoses.

The Problem

It is ten years since Kety and Schmidt (1948) devised their technique for determining *quantitatively* the total cerebral blood flow in man; and it is at first sight surprising that such an achievement should not have lent itself more fruitfully to the investigation of those vascular disorders of the brain which, owing to cerebral angiography, have achieved such prominence during the same decade. The reason is that estimates of *total* cerebral blood flow help us little in our efforts to evaluate the *regional* changes in flow which are a feature of conditions such as carotid thrombosis (and ligation), cerebral arterial spasm and arteriovenous fistula. The *qualitative* nature of these changes is being increasingly

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appreciated through the study of cerebral angiograms in man, while cerebral blood distribution in general has been the subject of experiments in the rabbit (McDonald and Potter, 1951). The gaps that now require bridging are those between quality and quantity, and between total and regional cerebral blood flow.

It was felt that if even rough estimations were to be made of the reduction in blood flow that might be occurring in particular arteries as the result of their spastic narrowing, some insight could perhaps be gained into the redistribution of cerebral blood flow during this pathological state. It seemed possible, moreover, that this might be a step towards the indirect measurement of these regional changes in blood flow within the complex anastomotic framework of the cerebral arterial system.

Cerebral Arterial Spasm

It is now well known to those familiar with cerebral arteriograms that reversible narrowing of certain cerebral arteries may occur in association with subarachnoid hæmorrhage. This is usually, but not invariably, a result of the rupture of an adjacent "berry" aneurysm. Pickering (1951) has discussed the semantics of the term, spasm, which will be used here to indicate this particular form of reversible narrowing, although its precise mechanism is still in doubt. The phenomenon was demonstrated in 1950 to the 6th International Congress of Radiology in London by Reid, Johnson and Ollerenshaw; it was described in some detail by Ecker and Riemenschneider (1951), and more recently by Johnson, Potter and Reid (1958), and by Gillingham (1958).

Material, Method and Results

7 patients suffering from subarachnoid hæmorrhage underwent cerebral arteriography, both while the arterial spasm was present and again later when the affected arteries had returned to what might be considered their normal calibres. At each occasion, the internal diameters of these arteries were measured on the radiographs and the decrease in the lumen due to the spasm noted. The expected reduction in blood flow was then calculated in accordance with the D^4 law, assuming that the pressure gradient, blood viscosity and length of the artery had remained constant.

Measurements were taken to the nearest half millimetre, and then corrected for the projection of the radiograph. The possibility of errors due to high contrast (Spiegler *et al.*, 1957) was borne in mind.

The results shown in the table indicate that reductions of blood flow might be expected to occur in the affected arteries of from 25-fold through a spastic internal carotid artery (Case 5) to as much as 400-fold in the case of a grossly narrowed anterior cerebral artery (Case 2). The degree of narrowing (from 1·5 mm. to 0·65 mm.) of the anterior cerebral

TABLE

Patient	Artery	Internal diameter (mm.) In spasm	Internal diameter (mm.) Afterwards	Reduction in blood flow during spasm
1 K. S.	R. Anterior cerebral	0·65	1·5	28-fold
2 J. L.	L. Anterior cerebral	0·4	1·9	400-fold
3 G. T.	L. Internal carotid	1·0	3·0	80-fold
4 E. P.	L. Anterior cerebral	0·65	1·5	28-fold
5 V. P.	L. Internal carotid	1·25	2·75	25-fold
6 A. M.	L. Anterior cerebral	1·25	3·0	33-fold
7 V. K.	Both Internal carotids	1·0	2·5	38-fold
		1·0	2·5	38-fold

artery in Case 1 (fig. 1) represents approximately a 28-fold reduction in blood flow. Where the main branches of the internal carotid artery have been involved with their parent in the spastic process, only the measurements of the carotid itself appear in the table.

Case 7, V. K. (figs 2, 3 and 4), where there was a symmetrical degree of spasm affecting each internal carotid and its main branches, is of special interest and will be discussed in detail. I am grateful to Dr. John Hirst of Oldham for referring this patient.

CLINICAL EFFECTS OF SPASM

Blood Pressure

Whatever might be expected on theoretical grounds, no consistent change in brachial arterial pressure was observed during the period of spasm. It is well known that there is frequently a moderate increase in, particularly the systolic, blood pressure for a variable period immediately following subarachnoid hæmorrhage, and this seems to occur whether or not spasm is demonstrated. There may also be lability of the blood pressure, but whether this is associated with a fluctuating degree of spasm it is not possible to say, for the arteriographic appearance represents only a split-second in the life of this pathological process.

There is no evidence here, therefore, that the narrowing of these cerebral arteries has any direct effect on the blood pressure. A greater influence in this direction might be the disturbed autonomic function that may occur, particularly in the case of an aneurysm rupturing in the region of the hypothalamus.

Abnormal Neurological Signs

These will be discussed briefly in relation to the still widespread, but probably erroneous, belief that "vasospasm" (the type of vessel is not specified) is responsible for the appearance of transient but frank neurological signs in circumstances other than subarachnoid hæmorrhage. It is therefore interesting to note that demonstrably severe arterial spasm may occur with very little clinical neurological abnormality, or with signs which might be considered inappropriate to the arteries affected.

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Thus, Case 7, V. K. (figs. 2, 3 and 4), who had marked spasm of both internal carotid arteries intradurally and of the proximal parts of both anterior and middle cerebral arteries, was rational and showed only a mild left hemiparesis and hemihypæsthesia, which included the face.

Case 6, A. M., who had marked spasm of the proximal part of the left anterior cerebral artery and of the left internal carotid, showed a well-marked left (ipsilateral) hemiparesis, with hemihypæsthesia and hemianopia. He recovered to a considerable and useful degree, and was uninterrupted in this course by the left common carotid artery being ligated. He had an aneurysm of the anterior communicating artery which filled from the left side.

In Case 2, J. L., there was a very marked narrowing of the left anterior cerebral artery, leading to an anterior communicating artery aneurysm. There was slight spasm of the left middle cerebral artery, but none of the internal carotid. His only abnormal neurological sign was some left (ipsilateral) facial weakness.

Case 5, V. P., showed spasm of the left internal carotid and of the middle and anterior cerebral arteries, but she had also had a large hæmorrhage into the left temporal lobe which alone would have been sufficient to account for the severe aphasia, right hemiplegia, hemianæsthesia and hemianopia that were present.

The remaining three patients showed various degrees of hemiparesis, contralateral to the spastic arteries, and in these cases there was no other obvious explanation for these abnormal signs. It is interesting that patient No. 4, E. P., also showed continuous improvement of a right hemiparesis despite ligation of the left common carotid artery, but she died later from recurrent hæmorrhage.

Thus, although it appears that arterial spasm alone may be associated with "appropriate" neurological signs, other factors, such as an intracerebral clot may also be present. The presence of ipsilateral signs has no satisfactory explanation. The availability, the efficiency, and the behaviour of the collateral circulation must also be important considerations, and these will be discussed.

Discussion on the Implications of Case 7

In Case 7, V. K. (figs. 2, 3 and 4), the patient was a housewife, aged 32, who had sustained two episodes of subarachnoid hæmorrhage in three weeks. A week after the second episode, bilateral carotid arteriography showed spasm of both internal carotid arteries and of the proximal sections of both middle and anterior cerebral arteries. (In this case, no aneurysm or angioma was demonstrated and no other cause was found, but vertebral angiography was not performed.) Six weeks later, the arteriograms were repeated and showed that the affected arteries had expanded to even, and presumably normal, calibres. The internal

carotid had on each side been reduced from 2·5 mm. diameter to 1·0 during the period of spasm, representing an estimated 38-fold reduction in blood flow to each carotid territory.

Now the *normal total cerebral blood flow* in man, according to Kety and Schmidt (1948) is approximately 740 ml. per minute for a 1,400 g. brain. Suppose this to be so in the present case, and that the blood is normally apportioned, in accordance with the D^4 law, as follows: *each carotid* (2·5 mm. diameter) carrying 180 ml. per minute; and the *basilar* (say, 3·0 mm. diameter—an average taken from 74 vertebral arteriograms —Potter, 1957) carrying 380 ml. per minute.

If the carotids are then constricted by spasm to 1·0 mm. diameter, they will each carry only approximately 5 ml. per minute, leaving some 730 ml. per minute to be taken by the basilar, if it is assumed that the total blood flow has remained the same. But here the D^4 rule (*or whatever factor one uses*) cancels itself out, as it were; because the basilar would need to expand only from 3·0 mm. to rather less than 3·7 mm. in order to accommodate this great excess of blood flow.

Can it and does it do this? In the present series of cases, there has been no vertebral arteriography to tell us the actual calibre of the basilar artery during carotid spasm and afterwards. There was, for what it may be worth as evidence, a small increase in the diameter of the *occipital* artery in three cases during the period of spasm of intracranial arteries on the same side (figs. 1 and 4). This was not, however, present in all cases, but it might mean that collateral channels, which perhaps included the basilar, had opened up; one can say no more than this.

More significant, perhaps, are observations that have been made on the power of the rabbit's basilar artery to dilate under somewhat similar circumstances. When both common carotids were occluded, the basilar dilated up to as much as 50 per cent of its resting diameter. It took from two to fifteen minutes to achieve the maximum effect, and then returned slowly to approximately its previous calibre after the carotids had been released (McDonald and Potter, 1950—unpublished observations). From these results, one might expect that a dilatation of less than 25 per cent would be at least within the competence of the same artery in man.

These experiments suggest that when the carotids are occluded, the brain, in the rabbit at any rate, needs that balance of blood and that the basilar is capable of carrying it. Is 740 ml. per minute necessary for the overt functioning of the human brain, or is it an over-generous supply? Finnerty *et al.* (1954) noted stereotyped signs of cerebral ischæmia (sighing, yawning, staring and confusion) during drug-induced arterial hypotension in 37 subjects, who had earlier remained alert despite a mean cerebral blood flow equivalent to 615 ml. per minute for a 1,400 g. brain. They concluded that "apparently significant reductions in

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cerebral blood flow from normal are possible without inducing manifestations of cerebral ischæmia". The mean value for the production of the signs of ischæmia was the equivalent of 440 ml./min./1,400 g. Kety *et al.* (1948) found, in cases of increased intracranial pressure, that all patients with a blood flow below 560 ml./min./1,400 g. were in coma. These were, however, tumour cases, so that the discrepancy between this figure and that for the hypotensive patients may have been due to factors other than general blood flow reduction. It seems clear, however, that a 40 per cent reduction in cerebral blood flow is possible without clinical evidence of ischæmia.

To return to V. K.: even if we assume that she had almost reached the critical level of reduced cerebral blood flow of some 440 ml. per minute, an additional 50 ml. per minute would still be required from the basilar. Could this blood reach those marginal regions of the brain which are normally the responsibility of the carotids? The anastomotic channels of the circle of Willis, the posterior communicating arteries, lead only to the spastic arteries, and we believe from the arteriograms that it did not go that way; for there was no encroachment by the vertebral-basilar system beyond the posterior communicating arteries, indicating that the pressure relationship between the two systems was essentially unchanged at this level. It could, however, go through the small peripheral arteries that connect the posterior cerebral arteries with the middle and anterior cerebrals.

The possible importance of these "somewhat neglected meningeal arterial anastomoses" has in recent years been emphasized by several writers, notably Vander Eecken and Adams (1953), Brain (1957) and Meyer (1958). Vander Eecken and Adams, in an admirable paper, review previous opinion on the functional significance of this system of arteries. The dispute on this subject between Heubner (1872, 1874, 1877) and Duret (1874) has also been discussed by earlier writers (Charcot, 1883; Beevor, 1909). In so far as the anastomoses on the brain surface were concerned, there were two distinct issues. First, Heubner considered the communicating arteries between anterior, middle and posterior cerebral arteries to be at least 1 mm. in diameter, and of importance as a means of collateral circulation; whereas Duret thought them to be much smaller than this, and was not impressed by their possible usefulness. In this, Charcot supported his protégé. (Too much attention should not be paid to the diameters of dead arteries, as Vander Eecken and Adams point out; they found these anastomoses to vary between 200 and 610 microns). A second bone of contention was the anastomoses in the leptomeninges *between contiguous branches of the same cerebral artery*, which were described by Heubner, but whose existence Duret denied; Beevor's attempt to solve this problem gave inconclusive results, in spite of which he found himself agreeing with Duret. Vander

Eecken and Adams, however, found this type of anastomosis, but only rarely.

Today, Heubner emerges relatively well out of all this, but he was not, as boldly stated by Vander Eecken and Adams, the first to describe these anastomoses in the meninges. Duret himself mentions some earlier anatomists who were familiar with them, and of these Haller (1754, 1808) gives a precise account. But no one seems to have included Willis (1664, 1684), whose view of the anastomotic arterial systems of the brain appears to have been as comprehensive as that of almost anyone since his time and was not confined to the circle that bears his name. One of his several passages on the pial arteries is better quoted in its original (1664), the possibility of ambiguity being thereby more fairly judged than if Pordage's translation (1684) is given; for it is perhaps easy to read too much into what he says:

"Circa haec vasa sanguifera, piam matrem obducentia, observamus, arteria et venas, dum a sinibus oppositis prodeuntes, invicem occurrunt, non modo per singulares propagines mutuo inosculatas, sarcinam suam immediate transferre, uti in aliis corporis partibus fieri solet; sed varie complicata et intertexta, ubique plexus admirandos constituere, . . . "

These peripheral anastomotic arteries may therefore be of some importance in the case of V. K. Very little dilatation would be required to enable them to carry the extra blood from the basilar, and they would deliver it directly to those adjacent parts of the brain deprived of carotid blood. I think it very likely that this happens; it would explain why the blood from the vertebral-basilar system (as judged by arteriography) so infrequently moves forwards beyond the posterior communicating arteries, even when the carotid supply is considerably restricted—it is probably easier for this system to send its re-enforcements "over the top." It would also explain why there is quite often in carotid arteriograms poor filling of the most peripheral branches of the middle and anterior cerebral arteries when there is spasm proximally. This is indeed due to the spasm: not so much because the contrast medium cannot quite reach its normal periphery, but rather because it is being kept out by the anteriorly moving blood from the posterior cerebral artery.

These mechanisms provide no obvious comfort for the *central arteries*, particularly those arising directly from the proximal parts of the anterior and middle cerebral arteries which are so commonly affected by spasm. No known anastomoses are available, but, unless they are severely distorted, these branches, having first call on such blood as finds its way along the parent artery, may not after all fare too badly since the parent is no longer so concerned with passing blood on to its usual territory distally, this having become another's responsibility.

It is necessary in discussing these matters to stress the importance of

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an adequately complete circle of Willis. Had one of V. K.'s posterior cerebral arteries been poorly developed in that part connected to the basilar, she might well have shown more neurological abnormality; for there would have been difficulty in getting blood in quantity from the basilar to the distal carotid areas on that side.

So, before neurological signs can with confidence be attributed entirely to the presence of spasm, the anatomical state of the circle of Willis must be known, together with patency of the carotid and vertebral arteries, proximally as well as distally. Also, we should like to know what the blood pressure *has been* since the episode of subarachnoid hæmorrhage, as well as what it is at, say, the time of arteriography; for the available anastomoses, and such power as these arteries have of dilatation, may not be adequate in the face of an episode of arterial hypotension. For all that is known, cases in which severe arterial spasm has been demonstrated as the only satisfactory explanation for a residual neurological deficit may have had such a fall in blood pressure early in their illness, and this may have combined with the narrowed arteries to cause a period of irreparable ischæmia within the territory of any spastic artery. It is of course unlikely that all this information could be obtained, but if such theoretical possibilities exist, they should not be disregarded.

Future Investigation

It is now possible to envisage a system of investigation which would test the validity of some of these speculations and provide data for a more accurate picture of any blood redistribution occurring during localized arterial spasm. By performing vertebral arteriography both during and after spasm, the true calibres of the basilar artery would be obtained in place of those that have been guessed here. And if total brain blood flow measurements were to be done, it would be seen whether there is any overall reduction in blood flow during the period of spasm, or whether the normal flow is maintained. It is hoped that opportunities will arise for all this to be done.

Summary

(1) Attention is drawn to the great influence of the calibre of an artery on the volumetric rate of blood flow through it.

(2) Measurement of total cerebral blood flow gives no indication of the presence and degree of regional changes in flow, whereas cerebral angiography gives qualitative information concerning such changes.

(3) The localized cerebral arterial spasm that may accompany subarachnoid hæmorrhage has been demonstrated arteriographically in 7 cases, and was later shown to have disappeared.

(4) The internal diameters of the affected arteries, while spastic and afterwards, have been measured on the radiographs, and the reduction

in blood flow that might have been expected to result from the spasm calculated on the assumption that blood flow is proportional to the fourth power of the arterial diameter. Other factors involved in Poiseuille's law were assumed to have remained constant. A reduction in blood flow of 25-fold to 400-fold was estimated to have occurred in the affected arteries.

(5) No consistent change in brachial arterial pressure was observed in association with the presence of cerebral arterial spasm.

(6) Abnormal and "appropriate" neurological signs were seen in three cases showing spasm. In two others the abnormal signs were ipsilateral to the spasm; in one other, there was a large temporal intracerebral clot as well as spasm to account for severe signs; and in one case with marked bilateral carotid spasm, there was only a mild left hemiparesis and hemihypæsthesia. Other factors should therefore be considered before abnormal neurological signs are attributed entirely to spasm.

(7) Calculations in the last case suggested that the basilar artery might be required to transmit an enormous excess of blood if it were to compensate for the carotids' deficiencies; but that the dilatation required of it for this purpose would be relatively slight and probably well within its competence.

(8) The possible importance of the small peripheral anastomotic cerebral arteries is considered in connexion with the conveyance of this blood from the basilar artery to the fringes of the carotid territory.

(9) A system of investigation is proposed which should indicate the quantitative changes that occur when there is redistribution of blood due to cerebral arterial spasm.

Acknowledgments

I am grateful to my colleagues, Mr. Richard Johnson and Dr. Reginald Reid, for access to much of the information on which this paper is based; and to my friend, Dr. Donald McDonald, for his critical scrutiny of the text.

Addendum

Since this paper was submitted, Case 7, V. K., has suffered, some eighteen months after her previous series of attacks, a further episode of subarachnoid hæmorrhage. Vertebral arteriography revealed an aneurysm at the origin of the posterior inferior cerebellar artery from the left vertebral. It was not possible to clip the aneurysm, and so the left vertebral artery was doubly ligated in its third part. This was well tolerated and she has returned home in good health.

The widespread and bilateral arterial spasm at the anterior end of the circle of Willis following the earlier hæmorrhages, which were presumably the result of the remote rupture of this, the only demonstrated, aneurysm, is of considerable interest. It would have been interesting

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also to have known whether there was any spasm of the vertebral-basilar system at that time.

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LEGENDS FOR PLATES

PLATE XXXIV

FIG. 1 (*Case* 1).—Right common carotid arteriogram (oblique view). A, The anterior cerebral artery (continuous arrow) is in spasm, and B, three weeks later, the same artery appears normal. An aneurysm of the posterior communicating artery has been clipped at its base in B. Note also that the tortuous occipital artery (interrupted arrow) seems larger in A than in B.

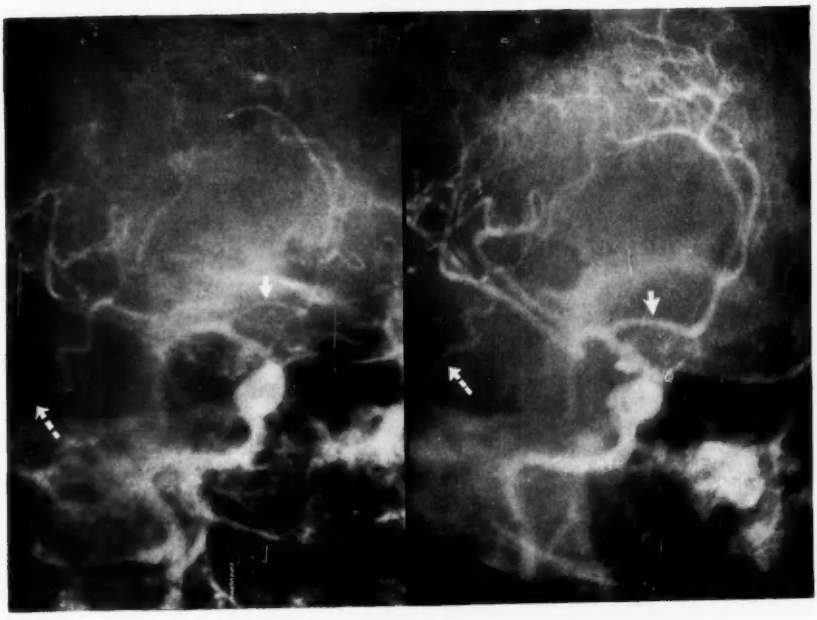
FIG. 2 (*Case* 7).—Left carotid arteriogram (antero-posterior view). A, Spasm of the internal carotid artery (continuous arrow) to 1·0 mm. diameter. B, Return to normal calibre (2·5 mm.) six weeks later.

PLATE XXXV

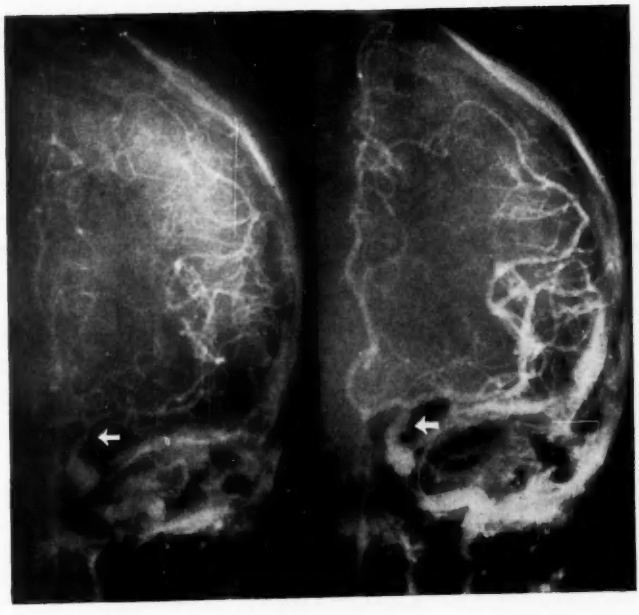
FIG. 3 (*Case* 7).—Right carotid arteriogram (antero-posterior view). A, Spasm of the internal carotid artery (continuous arrow) also to 1·0 mm. diameter. B, Return to normal calibre (2·5 mm.) six weeks later.

FIG. 4 (*Case* 7).—Right common carotid arteriogram (lateral view). A, Spasm of internal carotid artery (continuous arrow), and B, return to normal six weeks later. Note that as in fig. 1, the occipital artery (interrupted arrow) appears larger in A than in B.

PLATE XXXIV



A FIG. 1 B



A FIG. 2 B

To illustrate article by John M. Potter.

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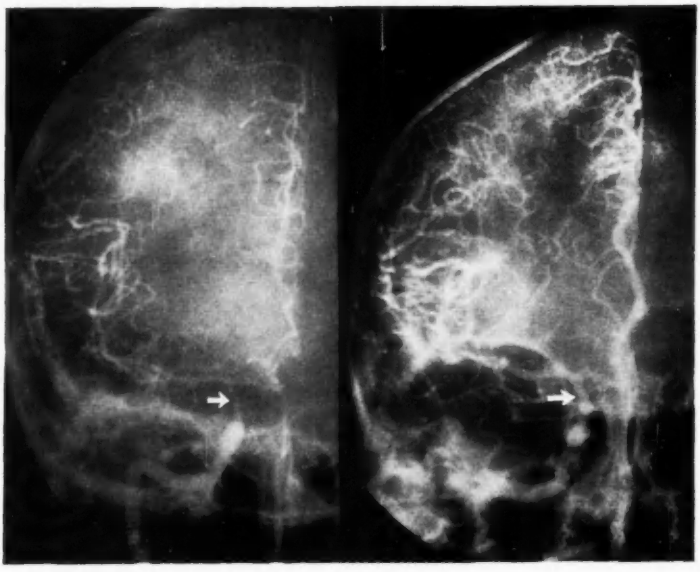
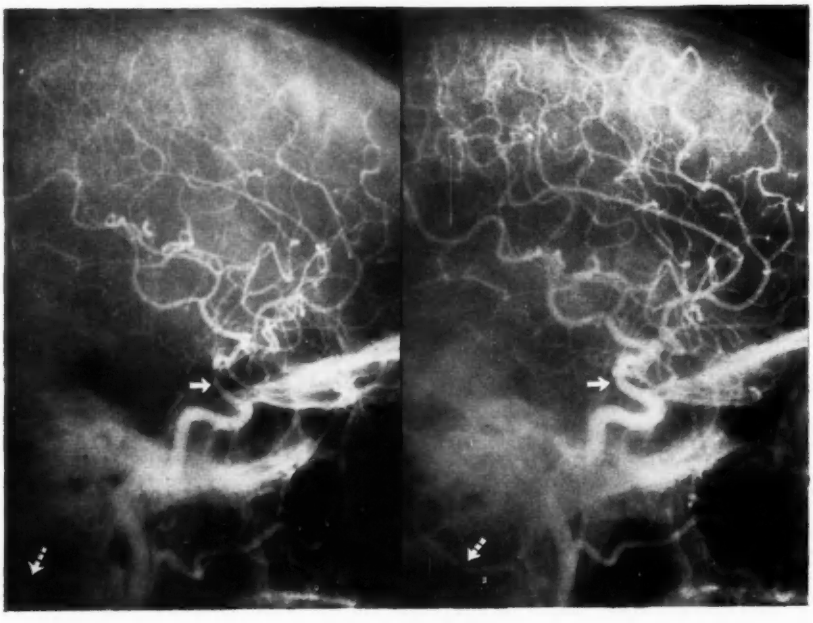
PLATE XXXV



A FIG. 3 B



A FIG. 4 B

To illustrate article by John M. Potter.

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THE VISUAL CHANGES IN TEMPORAL (GIANT-CELL) ARTERITIS.

Report of a case with autopsy findings

BY

M. R. CROMPTON

FEW reports of necropsies on cases of giant-cell arteritis have been published. In 20 published cases, in which the post-mortem findings have been reported, impairment of vision had been present on clinical examination in 8 cases, but histological investigation of the visual pathway in these was limited in extent. The main purpose of this paper is to describe a case of giant-cell arteritis with necropsy findings, in which a detailed histological examination of the visual pathway was made.

In 1935 Barnard described the post-mortem findings in one case, the clinical history of which included blindness, but it was Jennings (1938) who first recognized blindness as a complication of this condition. Blindness in one or both eyes is the most striking and often the most distressing manifestation of giant-cell arteritis, though as Meadows (1954) states, the patient sometimes shows a disproportionate lack of concern over this tragedy compared with the distress caused by the pain of the temporal arteritis. It may be that the cerebral ischæmia bestows a certain beneficial euphoria in these cases. Although visual deterioration occurs in about 30 to 40 per cent of cases of giant-cell arteritis and complete blindness in one or both eyes in 25 per cent, only 8 cases with visual defects have come to necropsy and have been published and in only 5 of these cases has necropsy shown involvement of the ophthalmic artery and its branches. Of the other 3 cases, 2 had giant-cell arteritis of the internal carotid arteries and 1 of both common carotid arteries. It is not stated whether the ophthalmic arteries were examined in these 3 cases.

The general pattern of visual involvement seems to consist of abrupt loss of vision in one eye, frequently followed by a similar loss of vision in the other eye a few days later. There is often very little to see in the optic fundus within the first few days or weeks. After fourteen to sixteen weeks optic atrophy supervenes, and the patient is finally left with the same loss of vision and pale discs. Visual disturbances of a transient

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nature, such as diplopia, sixth or third nerve palsies, or dimness of vision and grey spots before the eyes, have occurred in numerous cases. In a considerable number of cases these symptoms have been followed by blindness of remarkably sudden onset, sometimes occurring overnight in one or both eyes, or often following in a matter of hours after the onset of the initial symptoms of failing vision. The end-result may not be total blindness, but a field loss, which is very rarely homonymous but is often sector shaped with its apex centrally placed. This suggests a local, ischæmic lesion of the optic nerve.

In cases of giant-cell arteritis with visual involvement the optic fundus frequently presents an initial picture of slight or only moderate papillœdema with occasionally a few retinal hæmorrhages around the disc; later the optic disc becomes atrophic. In the case of Cardell and Hanley (1951), the ophthalmoscopic picture was one of occlusion of the central artery of the retina and vision was at first restored by the inhalation of amyl nitrite and massage of the eye. A similar ophthalmoscopic appearance was reported by Cohen and Harrison (1948, Case 3). Meadows (1954) mentioned one case with ophthalmoscopic evidence of bilateral central retinal artery occlusion with cherry-red maculæ. In the majority of cases, however, the fundus shows less change than expected in view of the severity of the blindness. This gross visual loss of abrupt onset with only slight changes in the fundus oculi may suggest a diagnosis of retrobulbar neuritis. The slight degree of papillœdema may possibly be accounted for by impairment of the return of blood in the veins as they lie in apposition to, or are crossed by, diseased arteries. Alternatively it may result from the increased permeability of the capillaries due to ischæmia, caused by the anoxia resulting from the initial arterial occlusion.

Case History

Mr. J. M. (Hospital No. 30753), a gardener, aged 71, was admitted to the National Hospital, Queen Square, on April 24, 1951, under Dr. F. M. R. Walshe and Dr. S. P. Meadows, complaining of blindness in both eyes. His vision had commenced to deteriorate on March 13, 1951. Apart from several minor injuries, he had always been in excellent health and had worked as a gardener until the onset of this illness.

Twenty years previously he had received a right fronto-parietal scalp wound as the result of a bicycle accident. It had not troubled him since.

His family history was non-contributory.

During Christmas 1950 he had an attack of "flu," which consisted of general malaise, fever and a mild frontal headache that had continued at intervals up to the time of examination. He could not relate the eye trouble to his headache.

He had attended an optician a week prior to the onset of his visual deterioration, not because of any change in his eyesight, but because he thought it was time to have his old glasses changed. He stated that on that occasion he could read "every line" of the optician's test chart.

Two days prior to March 13, he had been working with ashes and on March 13 he thought he had some ash in his left eye. There was no pain in the eye, but a "mistiness" of vision, which continued for two days as greyish-white patches before his left eye. The right eye was normal at this stage. He awoke on the morning of the 14th completely blind in his left eye. A week later, he noticed greyish-white patches floating around in front of his right eye. There was no pain. This condition cleared for an hour and then returned. On awakening the next morning he was completely blind in the right eye also. This complete blindness, without perception of light, continued unchanged afterwards. There had been no loss of weight or anorexia. He had some deafness in the left ear with occasional "buzzing." He did not know how long he had noticed the "buzzing."

On examination he was garrulous and his comprehension was limited beyond that attributable to his deafness, but he was willing and co-operative. His recent memory was poor, but his remote memory good. He did not look ill and looked years younger than his actual age. His blood pressure was 130/60. No abnormality was found in his cardiovascular system, respiratory system or abdomen. His temperature was normal. In the central nervous system, the only abnormalities noted were in his cranial nerves. There was no perception of light in either eye. The pupils were large and did not react to light or on convergence. There was a tendency for the eyes to deviate to the right, the right eye more so than the left. There were also some coarse nystagmoid jerks on looking to the right, more so in the right eye. He could not maintain his gaze to the left. He could not look up, but could look down. He could look up and to the left, but not up and to the right. It is possible that these defects of ocular movement were a result of the blindness, and poor co-operation. There was a very slight right lower facial weakness. Hearing was decreased to whispered voice in the left ear. Weber's test was referred to the left and Rinne's test was positive on both right and left. The abdominal reflexes were absent in all four quadrants. Examination of the ocular fundi showed that the right disc was pale and slightly swollen, with hæmorrhages around it. The left disc was paler than the right and slightly swollen, with hæmorrhages on the nasal side. In both eyes the arteries were thickened and contracted near the disc and enlarged further from the disc. There was narrowing of the veins at the arteriovenous crossings. The blood appeared to be flowing slowly in the veins of the left fundus. The temporal arteries were non-pulsatile and thickened and could be rolled under the finger, but were not tender.

On May 9, 1951, two weeks after admission, he was very confused and disorientated. The skin over one of the temporal arteries was slightly red. Four days later, on May 13, 1951, he became much more confused and restless. He sat up and complained of indigestion, holding the left side of his chest and died, two and a half weeks after his admission, and eight weeks after the onset of his blindness.

Investigations

On admission on April 26, the urine showed a faint trace of albumin and very occasional leucocytes and red cells were present. No casts were seen. On April 26 an X-ray of the skull showed the pineal to be calcified and within 2 mm. of the mid-line. Some calcification in the plane of the pituitary fossa was seen which was probably calcification in the internal carotid artery. On April 27 a red blood cell count showed 4,280,000/c.mm., the hæmoglobin was 76 per cent, the colour index was 0·88, and the white blood count was 5,600/c.mm., with a differential

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count of polymorphs 79 per cent, lymphocytes 19 per cent and eosinophils 2 per cent. On April 27 the E.S.R. was 45 mm. in one hour. On May 2 (*nine days after admission*), the lumbar C.S.F. was of normal pressure and content. The W.R. was negative in the blood and C.S.F. On May 7 (*two weeks after admission*) the E.S.R. was 49 mm. in one hour.

Post-mortem Findings

Necropsy by Dr. W. Blackwood.

At necropsy, both temporal arteries were pale, gelatinous, thickened and solid looking cords. Histologically they were seen to be severely involved by giant-cell arteritis (fig. 1). There was almost complete occlusion of the lumen by tissue consisting of fibroblasts, lymphocytes and plasma cells in a faintly basophilic matrix. The internal elastic lamina was broken up into short lengths. There were numerous multinucleated giant-cells in the media, some of which were closely applied to the disrupted internal elastica. In addition the media was infiltrated by lymphocytes and plasma cells and there were degenerative changes of the smooth muscle. There was an increase of collagenous tissue in the outer portion of the media and there was a thickening of the adventitia by an increase of collagenous fibrous tissue.

On examination of the carotid and vertebral arteries both common carotid arteries were healthy. The internal carotid arteries were healthy in the neck, apart from a ring of atheroma near the origin of the artery on the right side. The carotid syphons were atheromatous, partly calcified and dilated, especially on the right side. The external carotid arteries showed old, pale and almost total solidification of some of their main divisions due to severe involvement by giant-cell arteritis. The vertebral arteries, just after their origin from the subclavian arteries, were swollen and only a narrow channel passed through the pale, greyish mural thickening. Their course within the vertebræ was not examined, but in the region where they pierced the dura, at the level of the upper border of the atlas, they were swollen and severely narrowed for the next 5 mm. The condition appeared more recent and severe on the right side. At all these points of severe narrowing, the vertebral arteries were severely involved by giant-cell arteritis.

In the central nervous system, the cerebral blood vessels appeared healthy except for the changes already described in the vertebral arteries just after they pierced the dura. Also one of the smaller cortical branches of the posterior cerebral arteries showed perivascular and adventitial infiltration by lymphocytes, with only slight intimal hyperplasia. In addition there were two small arteries, one of them in the roof of the fourth ventricle and the other in the leptomeninges of the lower half of

the medulla, that were surrounded by lymphocytes and plasma cells and showed slight fibroblastic thickening of the intima.

In the examination of the central nervous system, apart from the visual pathways, the only significant findings were in the cerebellum and brain stem.

In the cerebellum there were parenchymal changes in both the lateral lobes and the vermis—being more pronounced in the vermis. These consisted of fairly well localized areas showing a diminution in the density of the granular layer, an increase in thickness of the Bergman astrocyte layer (up to 3 and 4 cells deep) and a great fall out of Purkinje cells. In some regions the Purkinje cells were completely absent, both at the bottom of the folia and on the surface of the cerebellum, and an occasional degenerate or vestigial Purkinje cell was present in other areas. In one dentate nucleus there was an absence of neurones and replacement by glial tissue in one area at its apex.

In sections through the pons, the only abnormality noted was the appearance of some shrunken, hyperchromatic nerve cells in the nuclei pontis.

In the medulla oblongata, similar, though less obvious, changes to those seen in the pons were present in the inferior olivary nuclei. Degenerate, ghost-like remnants of neurones were seen among the healthy neurones.

In the bodily organs, the heart revealed slight, focal myocardial fibrosis and the coronary arteries were greatly narrowed by giant-cell arteritis and not visibly affected by atheroma in the regions examined. In view of the sudden manner of death, the severely narrowed coronary arteries and the evidence of previous myocardial ischæmia, death in this case was probably due to myocardial infarction, but the rapidity of the terminal phase did not allow histological confirmation of this.

In the spleen, there was a definite excess of plasma cells and their precursors in the red pulp, especially adjacent to the trabeculæ. The splenic vessels were normal.

In the suprarenals there were foci of lymphocytes and plasma cells around the medullary vessels.

Histology of the Visual Pathways

Sections were taken through the following areas and stained by the techniques indicated:

The eyes and optic nerves (hæmatoxylin and van Gieson and Loyez). The optic chiasma (hæmatoxylin and van Gieson, Loyez, Methazol fast blue and cresyl violet and Holmes axon stain).

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The optic tracts, the lateral geniculate bodies, the optic radiations adjacent to the posterior horns of the lateral ventricles and the striate cortex (hæmatoxylin and van Gieson, methasol fast blue and cresyl violet, Holmes axon stain, and Scharlach R).

Left Eye and Optic Nerve

In the retina (fig. 2) there was an increase of fibroblastic and astrocytic nuclei in the nerve fibre layer but there was no noticeable narrowing of this layer. The material available, embedded in celloidin, failed to impregnate with silver and provide any information on the state of the axons in the nerve fibre layer. There was an almost complete fall out of ganglion cells and those remaining revealed severe degenerative changes. The nuclear, plexiform and rod and cone layers appeared normal. No marked changes were seen in the choroid. All the above changes were grosser on the nasal side of the fundus.

In the *nerve head* (fig. 3) the general appearance was that of optic atrophy with only slight œdematous swelling of the nerve fibre layer of the retina at the disc margins, mainly the nasal margin. There was infiltration of the branches of the retinal artery by lymphocytes and plasma cells in the adventitia and media and in some places this involvement extended over the edge of the disc. There was a hyaline appearance of the intima with an increase of intimal nuclei.

The optic nerve was narrow and atrophic. There was an increase of astrocytic and lymphocytic nuclei, especially behind the lamina cribrosa, an increase of fibrous tissue and fibroblast nuclei and thickening of the septa between the nerve bundles. Myelin stains showed evidence of the degeneration of myelin.

There was an involvement by giant-cell arteritis of the long and short posterior ciliary arteries and also of their branches in the arachnoid and pial sheaths. There was giant-cell arteritis of the arteries of the circle of Zinn, with narrowing of their lumina. There was complete occlusion of the ophthalmic artery by giant-cell arteritis, in a section through the posterior third of the nerve, with some attempt at recanalization of the organizing tissue. The retinal artery before it enters the optic nerve was narrowed by giant-cell arteritis (fig. 4) and there was organized and sometimes recanalized intimal thrombosis. There was perivascular cuffing of the retinal artery in its course within the optic nerve, but no occlusion was seen.

Right Eye and Optic Nerve

The same changes were seen as in the left eye, but they were less severe. A large branch of the central retinal vein on the nerve head was found to be flattened by the adjacent artery and mildly involved by a peripheral

lymphocytic cuffing. The adjacent branch of the central artery was involved by arteritis (fig. 5). This was a nasal branch of the artery which showed complete occlusion by fibrinoid, pink staining material undergoing early organization. There was considerable degeneration of the adjacent nasal retina.

Transverse sections through the optic nerve at the back of the orbit showed that the ophthalmic artery was involved by giant-celled arteritis, with narrowing of the lumen, but it was not occluded as on the left. Many of the small muscular branches of the artery were involved and some were occluded. The long and short posterior ciliary arteries (fig. 6) and the circle of Zinn were involved as on the left. There was perivascular cuffing of the retinal artery in its course within the optic nerve. Thus the distribution of vascular lesions was comparable to that on the left side.

The vessels in the sclera, ciliary body and iris appeared normal.

In both optic nerves, at a position midway between the back of the eye and the optic foramen, the nasal aspect of the nerve on cross section was more atrophic and the myelin more degenerate than the temporal side.

Optic Chiasm

There was evidence of proliferation of glial cells. Stains for myelin (fig. 7) revealed a generalized appearance of degeneration of myelin sheaths. As in both optic nerves, the nasal fibres showed a more severe degree of dissolution. Axon staining revealed widespread degenerative changes of the axons. The crossing nasal fibres were the worst affected. There was involvement by intimal hyperplasia and perivascular lymphocytic infiltration of numerous small arteries in the anterior and lateral angles of the chiasm. Also arterial involvement of the same nature implicated vessels in the centre of the chiasm (fig. 8) and both optic nerves immediately anterior to the chiasm. Many of these small arteries showed occlusion by intimal hyperplasia.

One of the arteries close to the pituitary stalk showed involvement by giant-cell arteritis. The lumen of the vessel was moderately narrowed. Evidence of infarction of the pituitary was not found in the sections examined.

Optic Tracts (at their origin behind the optic chiasm)

Evidence of gliosis was present but to a lesser degree than in the optic chiasm.

Scharlach R staining showed large amounts of sudanophilic material throughout the cross sections of the tracts, but it was denser on the infero-lateral aspect of the tract.

Myelin staining demonstrated generalized myelin degeneration. The

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central region of each tract, containing the macula fibres, was least affected, and the infero-lateral portion, containing the crossed nasal fibres (Greenfield and Epstein, 1937) was most severely affected.

Axon staining showed degenerative changes of the axons of varying intensity corresponding to changes in the myelin sheaths as described above. No abnormal vessels were seen.

The Visual Pathways Behind the Optic Tracts

The lateral geniculate bodies revealed a loss of neurones in all six layers and degenerative changes in many of those remaining. In the *optic radiations* and the *striate cortex* on both sides, no significant abnormalities were found. Fig. 9 summarizes the points at which there

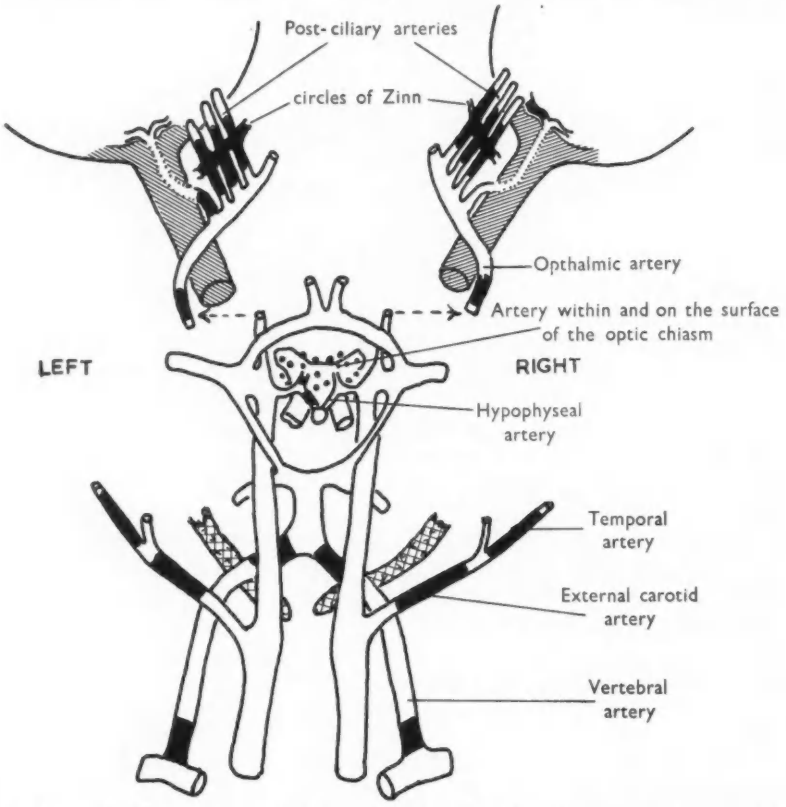

Fig. 9.—The blacked-in areas indicate the points at which there was severe arterial involvement by giant-cell arteritis.

was severe involvement of the arteries of the head and neck by giant-cell arteritis.

Discussion

Meadows (1954) puts the occurrence of ocular features at about 40 per cent and loss of vision in one or both eyes at about 25 per cent of cases. Harrison (1948) mentioned involvement of the eyes in 25 (33 per cent) out of the 75 cases he discussed, with permanent blindness of one or both eyes in 15 (20 per cent) of the cases. Cardell and Hanley (1951) state that 52 (37 per cent) of 137 recorded cases had visual symptoms and 36 (26 per cent) of these became blind in one or both eyes. Kilbourne and Wolff (1946) state that blindness occurs in 33 per cent of cases. Though blindness is a frequent accompaniment of giant-cell arteritis, the published cases in which disease of the ophthalmic arteries or their branches has been demonstrated at necropsy are only 5 in number. One of these was described by Cooke *et al.* (1946, Case 6) in which both retinal arteries showed involvement by giant-cell arteritic lesions with organizing thrombi. Cardell and Hanley (1951) described a case with right and left ophthalmic, left retinal and right posterior ciliary arteries involved. Greenfield (1951) reported a case in which the retinal and ciliary arteries of both eyes were the seat of intense giant-cell arteritis, involving all three coats and resulting in extreme narrowing of the lumen. There was considerable intimal thickening and lymphocytic infiltration of all coats, but mostly the adventitia, and the lesions extended into the scleral arteries some distance away from the disc. There was a fall out and shrinkage of ganglion cells in the retina, but otherwise the retina appeared normal.

Heptinstall *et al.* (1954, Case 14) describe bilateral ophthalmic artery involvement. Meadows (1954) briefly mentions the case which is now fully reported in this paper.

In this case, the visual system from the retina to the occipital cortex was examined, in order to find the position of the lesion or lesions responsible for the visual impairment and also to ascertain the extent of the involvement of the visual system. The retina of each eye showed atrophic changes similar to those found following ischæmia, when the cells most sensitive to a fall in the oxygen tension of the blood—the ganglion cells—atrophy and disappear (Duke-Elder, 1940). In each eye the fundal branches of the central artery of the retina were involved most severely on the nasal aspect of the nerve head, and this was associated with a greater degree of nasal retinal atrophy and a preponderant axon degeneration of nasal fibres which was traced back into the optic tracts. The presence of this pattern of axon degeneration, originating in the retina, indicates that the involvement of the retina was an important factor in the blindness.

The arterial blood supply of the retina and anterior one-third of the

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optic nerve is derived from two main sources. One source of supply is via the central artery of the retina and its branches to the innermost layers of the retina and the central core of the optic nerve. The other source of supply is from the posterior ciliary arteries and their branches to the outer layers of the retina and to the periphery of the optic nerve. The macula is supplied solely by the posterior ciliary arteries. The individual posterior ciliary arteries anastomose with each other anteriorly through the circle of Zinn. There is anatomically an anastomosis of capillaries between the retinal and posterior ciliary arteries but this anastomosis is not sufficient to prevent severe impairment of vision if either source is occluded.

Blindness can result from occlusion of the central artery of the retina or the posterior ciliary supply separately. This occurs, on the one hand, in embolism or in arteriosclerotic narrowing with thrombosis of the central retinal artery, and on the other, in arteriosclerotic obliteration and narrowing of the short posterior ciliary arteries and their choroidal branches and in arteriosclerosis of the small branches of the short posterior ciliary arteries supplying the optic nerve. Arteriosclerotic narrowing and obliteration of the ciliary arteries often occurs without any evident involvement of the central retinal artery. Where the central artery of the retina alone is known to have been involved, as in embolism and thrombosis, the abnormal ophthalmoscopic appearance has been prominent at an early stage, consisting of marked fundal pallor, grossly narrowed arteries, segmentation of the blood in the veins and a cherry-red spot at the macula. A similar ophthalmoscopic appearance has been seen in cases of giant-cell arteritis reported by Cardell and Hanley (1951), Cohen and Harrison (1948, Case 3) and Meadows (1954), where the clinical evidence was strongly in favour of blockage of the central artery of the retina alone. This contrasts with the fundal picture in cases of arteriosclerotic involvement of the posterior ciliary arteries and their choroidal branches without evident involvement of the central artery of the retina, as occurs in senile macular chorio-retinal degeneration in which the fundal changes may be practically absent for a considerable time, in the presence of severe deterioration in vision, or there may only be a slight pigmentation or an occasional small hæmorrhage adjacent to the macula. Also a widespread arteriosclerotic, obliterative process can occur in the small ciliary artery branches supplying the optic nerve, producing a severe visual defect with minimal or no fundal change and only much later resulting in optic atrophy. As Meadows (1954) suggested, involvement of the posterior ciliary arteries alone is as likely an explanation of those cases of giant-cell arteritis where blindness is associated with minimal initial, fundal lesions as is the explanation put forward that the block is in the central artery of the retina a considerable distance posterior to the eye or in the ophthalmic artery.

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In this case both sources of arterial supply were involved, but the ophthalmoscopic appearances and the histology indicate that though the involvement of the central retinal artery and especially its nasal branches, produced a major lesion, involvement of the posterior ciliary arteries and their branches was a significant factor in causing blindness.

The orbital part of the optic nerves was atrophic, partly due to degeneration of the axons of the ischæmic ganglion cells, but a considerable contribution to this atrophy must have been made by the ischæmia of the nerves themselves, because all sources of blood supply to the retina and optic nerves were grossly narrowed or obstructed. Thus it is difficult to be dogmatic as to whether ischæmia of the optic nerve or the retina was the most significant factor in the production of visual impairment.

Blindness occurred overnight in this case, and there are several similar cases with sudden loss of vision in one eye, perhaps occurring in a matter of hours, which has been followed a few days later by loss of vision in the other eye. In the present case, this might have been due to sudden thrombosis in the ophthalmic artery or its branches, or to slowing of the blood stream in them. The histological evidence was that of an organised thrombus in these arteries but we cannot tell whether it was originally formed suddenly. Recent, sudden, occlusive thrombosis does not appear to be common in giant-cell arteritis for the process of occlusion of the arteries appears usually to be a slow one, perhaps due to the combination of gradual deposition of fibrin and its organization, together with intimal hyperplasia and the recanalization of the resultant obliterative mass in some cases. The alternative explanation of the sudden onset of blindness overnight may be that gradual narrowing of the lumen by intimal thickening eventually reached such a critical stage that the increased sluggishiness of the blood flow during sleep was enough to go below the threshold of ischæmia and result in blindness on awakening. It is doubtful if spasm played a significant part, for the arteries were severely diseased and their muscular coats largely destroyed.

Although it is not thought to have been a precipitating factor in the onset of blindness in the case reported, disease of chiasmal vessels may well cause visual impairment. The blood flow through these vessels, which are all very small, may be impaired by even slight fibroblastic intimal hyperplasia of the intracranial portion of the internal carotid artery, which may be sufficient to block the mouths of the vessels that arise from it to supply the optic chiasm, such as the anterior superior hypophyseal artery, and the direct branch from the internal carotid artery. In the case reported, one of the superior hypophyseal and numerous chiasmal vessels were involved. Vascular lesions of the optic chiasm could probably be found in a large number of cases of giant-cell arteritis with visual symptoms. Cases such as that of

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Heptinstall *et al.* (1954, Case 7), with a stationary bitemporal field loss, could be explained as being due to a vascular lesion of the anterior chiasmal angle, or a more intense bilateral involvement of the nasal half of the optic nerve or the retina.

In the optic tracts and lateral geniculate bodies there was evidence of the continuity of the axon degeneration from the retinal ganglion cells, but no evidence of ischæmic changes, nor was there involvement of the vessels of supply. Ischæmic changes in the lateral geniculate body are very rare, possibly because it possesses a double blood supply, through the anterior choroidal artery and the posterior choroidal branches of the posterior cerebral artery (Abbie, 1933).

There was no significant abnormality in the optic radiations nor was there involvement, by giant cell arteritis, of the middle and posterior cerebral arteries which supply them.

Apart from lesions of the immediate arteries of supply of the visual system, such as the ophthalmic, middle and posterior cerebral arteries, vision may be impaired by arterial lesions at a distance, i.e. of the internal carotid and vertebral arteries, if the collateral circulation is ineffective. Occlusive involvement and narrowing of the internal carotids is a frequent complication of giant-cell arteritis and may result in symptoms and signs similar to those seen in carotid artery stenosis due to atherosclerosis (Symonds, 1955; Hutchinson and Yates, 1957) such as contralateral hemiplegia, aphasia, mental confusion and disorientation, hemianæsthesia, blurred patches before the eye and depression of the visual field in the form of a monocular central scotoma. If the mouth of the ophthalmic artery is patent and the lumen of the internal carotid artery is merely narrowed, these visual symptoms may be transient but, if the mouth of the ophthalmic artery is involved by the disease affecting the internal carotid artery or if the internal carotid artery is completely occluded, then permanent monocular visual defect or blindness may result. Such cases are those of Heptinstall *et al.* (1954, Case 12), in which both carotid arteries were involved and the patient showed blindness in the right eye and a central scotoma in the left eye. One of Meadows' (1954) 12 cases, all of whom had impairment or loss of vision in both eyes, died with a carotid occlusion and hemiplegia. In the case reported here the internal carotids were not blocked and there was no hemiplegia, but there was a local lesion in each retinal artery.

The extremely severe involvement of the vertebral arteries was probably the cause of the moderately severe cerebellar and minor pontine and medullary parenchymal changes. The absence of marked ischæmic changes in the occipital lobes suggests a good cardiac output and a good anastomotic or collateral circulation through the circle of Willis, or at any rate, to the posterior cerebral arteries. This is not surprising because, giant-cell arteritis being a subacute disease, it will usually allow time for

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the collateral circulation, if present, to become effective. If the cardiac output had not been so good, or the internal carotid arteries had not been patent, or a collateral circulation had not developed, then the severe vertebral involvement probably would have resulted in occipital infarction, as in the case of Heptinstall *et al.* (1954, Case 14), in which there was both severe vertebral involvement and thrombosis of the posterior cerebral arteries. Hutchinson and Yates (1957) in their concept of carotico-vertebral stenosis due to atheroma, stressed the dependence of the brain on the two internal carotid and the two vertebral arteries considered together as a functional unit and not as independent sources of vascular supply. The efficiency of this unit is affected as a whole, not only by the patency of the four main arteries but also by changes in the circle of Willis and the cardiac output. These principles will apply to giant-cell arteritis as they do to atheroma.

Of symptoms other than the blindness, the defects of ocular movement, if they were not due to the blindness, may be accounted for by involvement of branches from the ophthalmic arteries to the extra-ocular muscles and nerves, as suggested by Meadows (1954).

Summary

A case of giant-cell arteritis is reported in which bilateral blindness was the predominant and presenting symptom. There was involvement of ophthalmic, retinal, posterior ciliary, vertebral, chiasmatic, pituitary, suprarenal and spinal medullary arteries amongst others.

The involvement of the arteries of the pituitary, optic chiasm, medulla oblongata, suprarenal medulla and occipital cortex was unexpected and shows that this process affects small as well as large arteries.

The visual system was examined to determine the site and extent of involvement and the lesions primarily responsible for visual impairment. The retina and optic nerves were found to be severely affected by ischæmia as a result of giant-cell arteritis of the ophthalmic artery and its branches. This was the lesion responsible for blindness.

The less severe involvement of chiasmatic vessels is discussed and also the significance of the collateral blood supply in preserving the visual cortex in the presence of vertebral occlusion.

Acknowledgments

I should like to thank the Medical Committee of the National Hospital, Queen Square, for permission to publish this case. I am grateful to Dr. S. P. Meadows for access to the clinical records and Professor W. Blackwood for access to the pathological material and records and to both for their advice and constructive criticism. I am grateful to the technical and secretarial staff of the Department of Histology of the National Hospital, Queen Square, in particular to Mr. A. Greenaway, Mr. J. A. Mills and Miss J. Silverwood.

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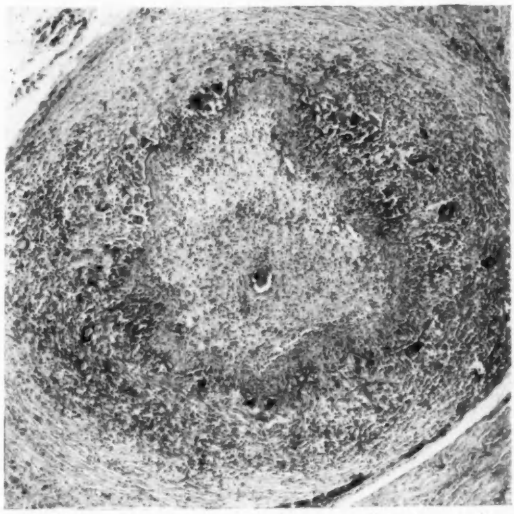

FIG. 1.—Giant-cell arteritis of a temporal artery with giant cells adjacent to the damaged internal elastica. The lumen is largely obliterated apart from a few recanalizing spaces. Hæmatoxylin and eosin. × 43.

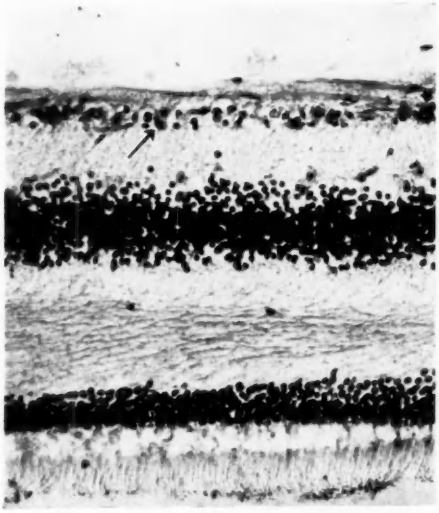

FIG. 2.—The retina with only a few degenerate ganglion cells remaining (arrow) and a great increase of fibroblastic and glial nuclei in the nerve fibre and ganglion cell layers. Hæmatoxylin and van Gieson. × 180.

To illustrate article by M. R. Crompton.

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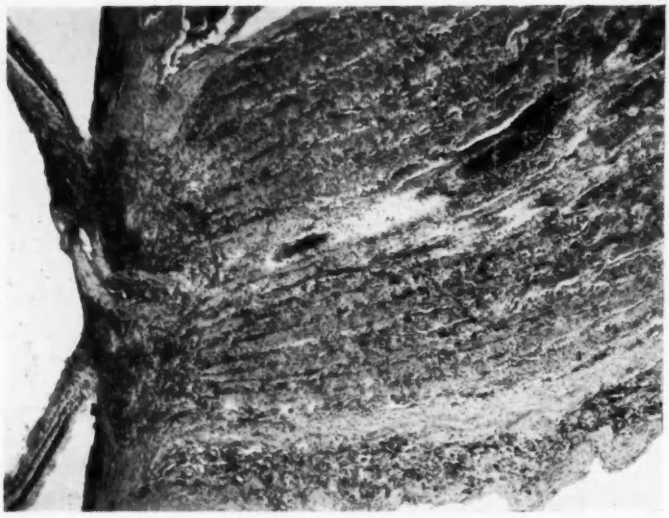

FIG. 3.—Optic nerve and disc of the left eye. The disc is atrophic. There is an increase of nuclei within the optic disc and nerve. The central artery of the retina is cuffed by round cells. Hæmatoxylin and van Gieson. × 26.

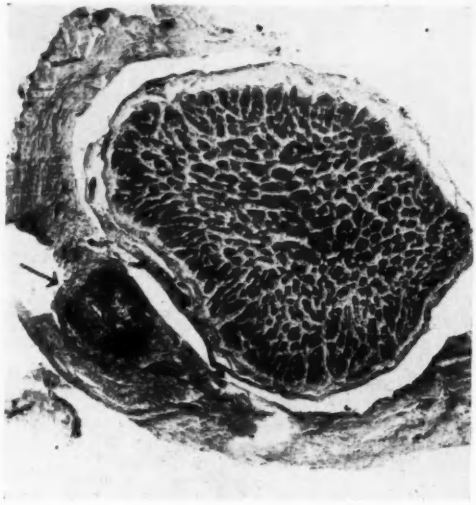

FIG. 4.—Posterior third of the left optic nerve with involvement of the retinal artery (arrow) by giant-cell arteritis. Recanalization has commenced. Hæmatoxylin and van Gieson. × 15.

To illustrate article by M. R. Crompton.

FIG. 5.—Nasal branch of the right central retinal artery with cuffing by round cells and occlusion by organizing fibrinoid material. Hæmatoxylin and van Gieson. × 308.

FIG. 6.—Giant-cell arteritic involvement of the vessels of the Circle of Zinn of the right eye. Hæmatoxylin and van Gieson. × 80.

To illustrate article by M. R. Crompton

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FIG. 7.—Degeneration and break-down of myelin sheaths in the optic chiasm. Loyez myelin stain. × 308.

FIG. 8.—Round cells cuffing a small, obliterated vessel within the optic chiasm. Hæmatoxylin and van Gieson. × 440.

To illustrate article by M. R. Crompton.

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ISOLATED TRIGEMINAL NEUROPATHY
A REPORT OF 16 CASES

BY

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ISOLATED lesions of the trigeminal nerve are usually held to be uncommon. Our experience of 16 cases in the past seven years, all but one of them seen in the Department of Neurology, Cardiff Royal Infirmary, suggests that they are not particularly rare, although the disorder has seldom been recorded in the literature.

Writing from his vast experience of trigeminal tic, Wilfred Harris (1935, 1950) has described 5 cases of neuralgia which were preceded by numbness of the face and trigeminal anæsthesia. In 1 of these, signs of disseminated sclerosis developed nineteen years later; but long follow-up of the remaining 4 revealed no evidence of systemic or other neurological disease. All of Harris' cases had sudden, painless loss of feeling in one side of the face which lasted weeks, months or years and which, after a varying interval, was followed by paroxysmal trigeminal pain similar to trigeminal neuralgia but lacking the characteristic triggers. He suggested that the initial lesion was an area of "neuritis" in the trigeminal sensory root analogous to the lesion of retrobulbar neuritis and quoted, as pathological support for his hypothesis, the case of Parker's (1928), in which a sclerotic plaque was found in the sensory root close to the pons. The paroxysms of pain did not begin before the facial numbness was regressing: this suggested to him that the pain was caused, in part at least, by stimuli arising distally in the jaws and teeth and passing through nerves made abnormally "irritable" by the neuritic process. A similar theory had previously been advanced by him to account for the paroxysms of trigeminal neuralgia itself. In further support of this he stated that pain in these 5 cases had been relieved by Gasserian injection, whereas he had found that facial pain arising from a central lesion was not relieved by this procedure.

None of the cases which we are describing developed the paroxysmal pain of trigeminal neuralgia, although at some stage of the disorder pain was a prominent symptom in 7 and severe enough in one to require

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sensory rhizotomy. In all our patients save 1, which we have classified separately, the predominant symptom was chronic, persistent sensory disturbance of the face, usually numbness in the territory of one or more divisions of the trigeminus. Our experience does not lead us to differ fundamentally from Harris' views on pathogenesis, although we shall give reasons for thinking that the site of the lesion may be at *any part* of the first sensory neurone of the fifth nerve in its extrapontine course. Recent confirmation of Harris' hypothesis of "neuritis" of the sensory root has come in the account published by Brodie Hughes (1958) of 3 cases of chronic benign trigeminal paresis on whom he had operated, expecting to find tumour. He found instead that the sensory root had been reduced to a few shreds which were embedded in thickened arachnoid up to the side of the pons.

Clinical Material

Between January 1951 and September 1958, 15 cases of isolated trigeminal dysfunction were seen in the Department of Neurology, Cardiff Royal Infirmary. One case (Case 13) was seen by one of us (C. E. C. W.) in April 1957 in the Department of Neurological Surgery, Newcastle General Hospital.

The record of clinical history and examination was available for all cases, together with standard radiographs of chest and skull, blood examination and serology. The abnormal findings were limited to the territory of the trigeminal nerves and, in a few cases, to the related autonomic nerves and to disorders of taste. These findings are recorded in Table I, pp. 394–395.

Infection of the paranasal sinuses was present in 4 cases (Cases 3, 5, 10 and 13); pus was aspirated at proof puncture from 2 (Cases 3 and 5) and in 1 case (Case 13) a Caldwell-Luc operation was performed.

3 patients had significant hypertension (Cases 1, 4 and 6) and in 1 of these (Case 1), who had been under hospital care for nephritis, albuminuria was constantly present.

Diabetes mellitus was present in 1 case (Case 9).

In 7 patients the sense of taste was impaired or lost on the side of the trigeminal lesion; in 1 there was gross disturbance of autonomic function on both sides of the face together with trophic destruction of the nose; and in 3 others there was a complete or partial Horner's syndrome. Their ages, at the onset of symptoms, ranged from 30 to 64 years; 11 patients were aged 40 or more years: 6 were male, 10 female.

Follow-up of these cases has varied from a few weeks to 9 years. The shortest interval between the onset of symptoms and the last follow-up examination was fifteen months; the majority were followed for at least three years from the start of their illness. 12 patients were investigated in hospital. All had routine radiographs of the skull including basal views to demonstrate the exit foramina of the lower divisions of the

trigeminal nerves. In 10 cases (Cases 2, 3, 4, 5, 6, 9, 10, 14, 15, 16) the cerebrospinal fluid was examined and was normal. The Wassermann reaction was negative in the blood in every case and in the C.S.F. of the 10 in which this fluid was examined. Carotid angiography on the side of the lesion and lumbar air encephalography were carried out in 2 cases (Cases 6 and 16) and were normal.

In 15 of the 16 cases the predominant lesion was impairment of sensation in the territory of one or more divisions of the trigeminal nerve. In 6 cases the lesion was on the right side; in 5 cases on the left; and in 4 cases lesions occurred on both sides. In a single case both motor and sensory functions of the left trigeminus were involved. This also differed from the others in running a rapid course to complete recovery within a year.

The essential data of our 16 cases are summarized in Table I. The histories and clinical findings of 2 are given in detail below: Case 10 was a typical example of trigeminal sensory neuropathy; Case 15 presented with unique trophic lesions.

Case 10.—*Female* (*age at onset*, 58)

This patient was an intelligent schoolteacher, a mathematics mistress, who was able to give an unusually clear account of her symptoms. During most of the ten months before she was seen by us she had been under continuous neurological review; the details of her story as related to us were confirmed by reference to the notes made during this time.

History.—In June 1957 she was driving in an open car when she experienced a peculiar sensation in her right cheek. She described this variously as a "prickling and burning," "as if stung by nettles," and a feeling as if her face were "stiff and distorted."

Several weeks later the right side of her tongue felt "burning," the upper and lower lips on the right were "oversensitive and felt sore" and the skin at the right angle of her mouth felt "cut." At about the same time, the inside of her right cheek and gums became "insensitive" and this interfered with her eating. (Numbness of her lower gums preceded that of the upper gums by a brief interval.) This was described "as if she had had an injection."

Early in August 1957 she consulted a dentist and the right upper premolar tooth was extracted without change in her symptoms. A week later she was referred to an aural surgeon: as a radiograph of her sinuses suggested antral infection proof puncture of the right maxillary antrum was carried out with negative findings. At this stage she was seen by a neurologist who found sensory impairment in the territory of the third division of the right trigeminal nerve.

By October 1957 the paræsthesiæ had extended into the right side of the nose and nostril and hypalgesia was present in the second and third divisions of the right trigeminal, including the upper and lower gums and the right half of the tongue. In the following month pain and temperature sensations were found to be returning to the anterior two-thirds of the tongue, where previously they had been grossly impaired although there was a persistent perversion of the response to cold stimuli which gave rise to painful "smarting" in this part of the tongue.

During the six months from June to December 1957 certain features of the paræsthesiæ were noticed. They were described as crescendo during the first two months, then static for three months before declining. They varied in the patient's awareness; they were never very noticeable when she was busy, coming on in moments of relaxation

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TABLE I.—CLINICAL DATA AND FOLLOW-UP OF 16 CASES OF ISOLATED TRIGEMINAL DYSFUNCTION

Details of sex, age, year of onset, initial and subsequent symptoms, and physical signs at time of examination are given. Where impairment of corneal reflex was only sign of first division sensory loss, this is recorded as (I). The duration is calculated from onset of symptoms to October 1, 1958, unless otherwise stated.

				Symptoms		*Signs*				
Case	*Sex*	*Age*	*Onset*	*Initial*	*Subsequent*	*Side*	*Division*	*Taste*	*Autonomic*	*Duration to October 1, 1958*
1	F.	41 years	1955	Pain	Numbness Irritation Pins and Needles Scalding	R.	II. III.	N.	—	3 years
2	M.	40 years	1955	Numbness	Tingling Fullness of ear Electric shocks	R.	I. II. III.	N.	—	3 years
3	M.	51 years	1955	Numbness	Pins and needles	L.	II.	N.	Ptosis	3 years
4	M.	50 years	1952	Paræsthesiæ	Pins and needles Numbness	R.	(I) II. III.	N.	—	
					Tingling, burning, wetness, electricity	L.	(I) II. III.	N.	—	6 years
5	F.	54 years	1953	Pain	Numbness Smarting (Hyperæsthesia)	R.	III.	N.	—	5 years
*6	F.	55 years	1948	Pain	Frozen, tingling, stinging Numbness Warm and swollen Cold water	L.	I. II. III.	absent	Horner	10 years
7	F.	60 years	1956	Pain	Numbness Burning	R.	II. III.	absent	—	
					Tormenting	L.	II.	N.	—	2 years

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					Tormenting	L.	II.	N.	—	2 years
8	F.	—	1956	Pain	Numbness	L.	(I) II. III.	absent	—	2 years
9	F.	64 years	1954	Paræsthesiæ	Spider's web Numbness Elastic band Pain	L.	(I) II.	N.	—	4 years
10	F.	58 years	1957	Paræsthesiæ	Stung with nettles Prickling, burning	R.	II. III.	N.	—	
					Stiff and distorted Sore, smarting Dental injection Velvet	L.	II.	N.	—	15 months
11	M.	47 years	1949	Pain	Numbness, Deadness Horrid feeling	L.	I. II. III.	absent	—	9 years
12	F.	33 years	1954	Numbness	Felt dead Extra thick skin Electricity, aching	R.	II. III.	impaired	—	4 years
13	M.	39 years	1956	Numbness	Cold feeling Tingling	R.	II. III.	N.	—	2 years
14	F.	35 years	1955	Pain	Burning, tingling	R.	I. II. III.	N.	—	3 years
15	F.	58 years	1949	Numbness	Tingling, pain	R. L.	I. II. III. I. II. III.	absent absent	Horner xerophthalmia xerostomia	9 years
16	M.	30 years	1952	Numbness	Soreness Fullness of ear Pricking, pain	L.	(I) II. III. and motor	absent	ptosis	1 year (Full recovery) (1953)

**Case* 6.—Craniotomy and section of left trigeminal sensory root was performed by Mr. Charles Langmaid on 18.7.51.

and particularly in the early part of the day. They did not interfere with sleep. When experienced most intensely they seemed to spread all over the right side of her face, and into her scalp. They were always maximal around her lips and mouth.

In early January 1958 she complained of a "prickling sensation" over the *left* malar bone and in the following March impairment of sensation on the left cheek was first recorded. She had become aware of numbness of the left cheek at that time and described a zone, triangular in shape with its apex at the left angle of the mouth and base near left ear, "like the feeling in one's face after a dental injection before the face is quite numb." The tongue was not involved on the left side. The surface of her left cheek felt "like velvet" and on touching it with her fingers she felt nothing until she took her fingers away when she experienced "a sort of delayed sensation" of touch.

Pain had *not* been felt in any part of her face at any time since the onset of symptoms in June 1957.

Examination:

Motor: normal bulk and power of muscles innervated by trigeminus. Normal jaw-jerk.

Sensory: corneal reflexes equal.

Right: first division normal. Second and third divisions: impairment of pain sensation subjectively with an occasional objective mistake in immediate circumoral region; also an occasional light touch missed. No disturbance of temperature or of deep sensation. Upper gums numb to pin-prick; lower gums and right half of tongue normal. Persistent "burning" in right half of tongue, aggravated by extremes of temperature.

Left: first division normal. Second division: impairment of pain sensation subjectively with an occasional objective mistake in upper lip; also a few light touches missed in this area. No disturbance of temperature and deep sensations. Upper gums and inside of cheek normal. Third division: normal, including left half of tongue.

Taste: normal.

Autonomic: normal.

Case 15.—*Female* (*age at onset*, 58) (figs. 1 and 2).

This elderly woman was an extreme example of trophic lesions arising from anæsthesia in the distribution of the trigeminal nerve. Over the course of six years her nose became progressively eroded to the extent of complete destruction.

History.—Her illness began at Christmas 1949 with redness and pain of both eyes. She attended an ophthalmic clinic where a diagnosis of bilateral kerato-conjunctivitis (Sjögren's disease) was made. At about the same time a red, tender and painful sore developed at the edge of her left nostril. It increased slowly in size. In October 1950 she was seen by a dermatologist and a biopsy was taken. This showed a hyperkeratotic lesion with superficial inflammation but no evidence of neoplasm. The sore area continued to increase in size and the outer margin of the nostril gradually was eaten away.

In January 1951 both sides of her forehead became numb and six months later her left upper lip was also numb. She was unable to recognize the temperature of food in the left side of her mouth. Thereafter, numbness spread rapidly over the whole of the left side of her face and in August 1951 the same process affected the right side of her face. Her tongue and mouth became very dry at this point.

Examination in October 1951 showed bilateral kerato-conjunctivitis with small, irregular pupils and bilateral corneal opacities. Her left nostril was ulcerated (fig. 1A and B). There was no involvement of the motor root of either trigeminal, but both corneal reflexes were absent and the sensations of touch, pain and temperature were impaired in the first and second divisions on both sides, loss being absolute for all

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modalities on the left side. There were slighter changes, mostly subjective, in both third divisions. Taste was absent in the anterior two-thirds of the tongue.

By March 1957 her condition had steadily worsened. Her nose was now totally eroded and she was profoundly anæmic. She was almost blind: with the left eye she could just count fingers at the distance of one foot; with the right, only the difference between light and shade was perceived. She had difficulty in swallowing and had no sense of taste. Hearing was unaffected. Despite her affliction she remained alert, cheerful and uncomplaining. Neurological abnormalities remained restricted to the territory of the trigeminal nerves.

Examination (fig. 2A and B).

Motor: normal bulk and power of muscles innervated by trigeminals.

Sensory: corneal reflexes—right and left absent. First divisions (right and left): dense loss of tactile, pain and thermal sensibilities.

Second divisions (right and left): impairment but not absolute loss of these modalities.

Third divisions (right and left): subjective impairment, but no stimuli were missed with touch and pin-prick and thermal discrimination was intact.

Taste: absent (in anterior two-thirds of tongue).

Autonomic: bilateral ptosis with small irregular pupils; loss of secretions from lacrimal and salivary glands.

Sensory Neuropathy

Of the 15 cases with involvement of sensory function only, pain was present initially in 7. Numbness and various paræsthesiæ were early symptoms in the remainder. The speed of onset was open to some doubt: clearly an attack of pain would be remembered more distinctly than a vague numbness or tingling sensation. Hence the 7 patients whose initial symptom was pain all stated that the onset was abrupt, whereas of the others only 3 out of 9 described a sudden or rapid beginning of their symptoms. Whatever the mode of onset, in all cases loss of feeling or altered sensation in some part of the face came to dominate the symptomatology and in the majority it was the persistence of this which led to the patients' seeking medical advice.

Although most patients complained of numbness in the affected area, it became apparent on careful questioning that their complaint was as much of altered or abnormal sensation as of simple loss of feeling. This "positive" quality of their symptom often varied from week to week and hour to hour and was most obtrusive in leisure hours or times of fatigue: it was rarely severe enough to disturb sleep. In 9 patients the sensory loss within the mouth was so dense that it interfered with eating and the cheek was bitten (Cases 1, 2, 4, 6, 8, 10, 13, 15, 16) and 3 patients (Cases 6, 11, 15) found that they could touch their eyeball without blinking (fig. 3). In most, abnormal and unusual sensations were experienced early and intensely on cheek and chin and predominated around the mouth; in 6 burning or smarting sensations were felt in the tongue (Cases 1, 2, 4, 10, 12, 16). The variety and multiplicity of these paræsthesiæ can be seen in

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Table I, in which every *recorded* symptom of this kind is listed for each patient.

Numbness of the face in patients who had undergone some surgical procedure for the relief of trigeminal neuralgia was studied by Rowbotham (1939). He found that it was a complex sensation in which feelings of coldness and of swelling were important components, so much so that it was "difficult to persuade the patient that there is no visible or palpable swelling." He thought that the sensation was unlikely to be due to impulses arising in the fibres which accompany the facial or sympathetic nerves as it persisted after stellate ganglionectomy and in those cases in which the facial nerve was already "out of action." (This would not preclude the carrying of such impulses by fibres running in the accessory sympathetic chains of the neck which have been subsequently described by Guerrier, 1944.) Stimulation of the proximal end of the severed sensory root at operation had, in Rowbotham's experience, always given rise to pain and he concluded that it was unlikely for the sensation of numbness to arise at this site. The recent studies, however, of Weddell and his colleagues (Weddell, 1957; Lele and Weddell, 1956) throw doubt on the validity of this observation as these workers have shown that the quality of a sensation may be the function of a pattern of nervous impulses arising from free nerve endings in a given area at a certain frequency. The sense of swelling described by Rowbotham as a component of numbness was present in several of our patients. One described his cheek as "numb and puffed out" (Case 4); a female patient (Case 6) said that her face was "swollen," another (Case 10) that it was "stiff and distorted," and a third (Case 12) said that it seemed "as if there was an extra thickness of fat between my finger and the bone when I touch it." 2 patients (Cases 2 and 16) complained of a full feeling in the ear. On the other hand only 1 (Case 13) had a sensation of coldness, whereas half the patients made complaint of heat and warmth, or of burning or smarting. Several likened their feeling to a dental anæsthetic, one patient stating that it was "like the feeling in one's face after a dental injection before the face is quite numb" (Case 10). Similar dysæsthesiæ have often been described in patients who have undergone sensory root section for trigeminal neuralgia. In their follow-up of 338 survivors from a total of 553 patients who had undergone sensory rhizotomy, Peet and Schneider (1952) found that a high proportion had abnormal sensations, other than sensory loss, on the side of the operation: 213 (55·7 per cent) had "crawling and drawing" sensations: 116 (30·4 per cent) had burning pain; whereas only 16 (4·1 per cent) complained of numbness of the face.

By contrast with this rich variety of symptoms, the physical signs were stereotyped and sometimes surprisingly slight. In discussing the presentation of trigeminal neurinomas, Jefferson (1955) remarked that the signs of sensory loss in the face were usually not as severe as the patient's descrip-

tion had led the clinician to expect. The exclusion of this kind of tumour was a major diagnostic problem in our cases and is fully discussed in the differential diagnosis. The methods of sensory examination in our patients were the simple clinical tools of cotton-wool for light touch, pin-prick for pain and hot and cold tubes of water for thermal sense. Vibration was imparted by a standard tuning fork (C. 128°), the foot being placed on chin or over malar bone, and deep pressure was applied by the observer's thumb with some firm resistance inside the patient's cheek. Using these relatively crude methods, pain sense was more frequently affected than any other modality and analgesia was always denser than thermanæsthesia. (The dissociation, therefore, of pain and temperature impairment recorded in some cases, and of anæsthesia and analgesia in others, was not necessarily attributable to the pathological process.) In all cases deep pressure and vibration sense were normal.

Analysis of the results (Table I) showed that the second and third divisions were involved with about equal frequency (2nd division: 19 times; 3rd division: 16 times). By inclusion of impairment of the corneal reflex, a very sensitive sign without analogue in the lower divisions, the ophthalmic division was involved 11 times; but, if cases in which a sluggish corneal reflex was the only sign elicited of ophthalmic sensory loss were excluded from the tally, this division was found to be affected six times. From these figures it will be seen that the lower divisions were involved three times as often as the ophthalmic.

The finding of 7 cases with impairment or loss of taste on the affected side suggested that, at least in these cases, the lesion included the peripheral branches of the mandibular nerve so that the function of the fibres of the chorda tympani would be impaired along with that of fibres of the lingual nerve. But examination of the results of trigeminal rhizotomy shows that this interpretation *may* be false. Rowbotham (1939) quoted 107 patients who had had Gasserian ganglionectomy, as reported in the literature of half a century ago, in 61 of whom taste had been either impaired or lost. In his own series of 40 patients who had been subjected to a variety of surgical procedures he gave objective evidence of impairment of gustatory function in 34 patients, although no injury to the pathways of taste was known to have occurred. Discussing these findings Rowbotham suggested that the impairment of taste was a central disorder of perception rather than the peripheral loss of a specific sensation, the defect being due to the loss of the "background of common sensations" mediated through the trigeminal nerve. Harris' experience (1952) was similar. In his series of 2,083 cases of trigeminal tic treated by Gasserian injection he found over 200 in whom the sense of taste had been affected. Although in a few this hemiageusia was permanent, in the majority it was a temporary phenomenon lasting from days to years; between 30 and 40 cases had no gustatory disturbance following interruption of the third

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division, or total Gasserian destruction or sensory root section. Like Rowbotham he explained the ageusia by assuming "a correlation or welding of the sensibility of tongue and palate by the fifth nerve with the true gustatory sensations from the chorda and petrosal nerves," dysfunction of one part of which would affect the whole. Whether this is the correct interpretation or not, it is clear that alteration of taste sense may occur in patients in whom the recognised gustatory pathways are intact, but in whom there is a major lesion of the trigeminal sensory root.

Autonomic involvement was unusual and only severe in one patient (Case 15). Few, if any, autonomic fibres pass through the Gasserian ganglion; but each of the three sensory divisions receives its autonomic component as it passes through its foramen of exit from the skull. The cells of the ciliary and sphenopalatine ganglia are derived embryologically from the trigeminal ganglion by outward migration along the sensory divisions, but in the adult they are functionally independent of the trigeminus. The ophthalmic nerve, after passing through the wall of the cavernous sinus, leaves the middle fossa of the skull by way of the superior orbital fissure. Before it enters the fissure it divides into its three principal branches, the frontal nerve lying superiorly, the lacrimal nerve laterally and the naso-ciliary nerve infero-medially. The frontal nerve is entirely sensory: it divides into its terminal branches, the supra-orbital and supra-trochlear nerves, which supply the skin of the forehead. The lacrimal and naso-ciliary nerves, however, have dual functions. The former conveys both sensory fibres from the conjunctiva and anterior orbital tissues and, by virtue of its anastomosis with the zygomatic branch of the maxillary nerve, secreto-motor fibres to the lacrimal gland; the naso-ciliary nerve carries sensory fibres from the root of the nose and eyelids, from the mucous membrane of the external nares and from the tip of the nose and the ala nasi, and by the way of its ramus communicans with the ciliary ganglion it carries sympathetic fibres to the dilator muscles of the iris.

The progress of the disorder in our patient (Case 15) in whom autonomic involvement was most extensive can be followed against this anatomical background. Within a year of the onset she was seen in an ophthalmic clinic and found to have small pupils, ptosis, dryness of the ocular mucous membranes and an excoriation at the edge of her left nostril. Three or four months later, just thirteen months after the first ocular symptoms, she became aware of numbness of her forehead. Subsequently the neurological disease extended at increased tempo through all divisions of both trigemini. With these data it is possible to imagine a process beginning in the autonomic fibres themselves and spreading by contiguity first to the fibres and parent cells of the naso-ciliary and lacrimal nerves, then to the frontal nerve, later to the maxillary and mandibular nerves. With regard to tissue susceptibility to the particular pathogenic agent in this case, it might be significant that the cells of the ciliary and sphenopalatine ganglia

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are derived embryologically from the trigeminal ganglion. Were the process due to a neurotropic virus, it would be possible to visualize its slow, centripetal migration along these sensory nerves and its more rapid dissemination to other branches of the trigeminus after it had reached the Gasserian ganglion. When the patient was admitted to hospital in September 1951, the ocular disorder and erosion of the nose (the latter indicating dysfunction of the naso-ciliary nerve) had been present for twenty-one months, her forehead had been numb for nine months, her left cheek numb for three and her right cheek for one month: and at examination some degree of sensory loss was found in all divisions of both trigemini, maximal in the first and least in the third. The process had clearly speeded up after the forehead had become numb, lending support to the hypothesis that extension was facilitated by the proximity of structures in the Gasserian ganglion.

Trophic Lesions in the Trigeminal Field

Trophic lesions in the trigeminal field have been described as a complication of pathological processes involving both the first and second sensory neurones, but they are uncommon. Surgical division of the trigeminus either peripherally or by section of its descending root (Sjöqvist's operation) may give rise to a number of post-operative sequelæ which are related to these lesions. They will be considered first.

Herpes simplex occurs so frequently in the area made anæsthetic by surgery that we have known surgeons who look for this as the hallmark of a successful operation. This phenomenon has been studied by Carton and Kilbourne (1952) in a series of 17 patients who were undergoing sensory root section for trigeminal neuralgia. Lesions considered to be herpetic were seen on the lips of 16 cases within forty-eight to ninety-six hours of operation and in 5 of them also on the palate. Their site corresponded exactly to the area of selective denervation. In 8 cases the virus of herpes simplex was recovered from the ulcers. No lesions were seen in these 16 cases on the eye, pinna or tympanic membrane. Andrewes and Carmichael (1930) showed that most adults have antibodies to herpes simplex; nevertheless local outbreaks of the disorder occur despite circulating antibodies. According to Braley (1952) the neutralizing power of the serum decreases during manifest herpes and increases again during convalescence. Presence of antibody may in part account for the difficulty of isolating the virus from tissues in which it has been suspected. In 2 patients who developed labial lesions Carton and Kilbourne failed to isolate the virus from ganglion tissue removed at the time of operation; but as Behrman and Knight (1954) pointed out, this failure might have been due to contamination with antibody.

After herpes, neuropathic keratitis is the commonest complication of trigeminal sensory rhizotomy. In their series of 553 cases Peet and

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Schneider (1952) reported keratitis in 84: although it constituted "no problem" in half of them, in 43 tarsorrhaphy was necessary and in 1 patient the eye had eventually to be enucleated. The ætiology of this keratitis is unknown; it has been attributed to an insensitive cornea, following section of the ophthalmic fibres, and to failure of tear secretion which could result from injury to the great superficial petrosal nerve. This latter result is not invariable as the bulb can be kept wet by the secretion of other glands in the lids (Cawthorne, 1954). Dott (1951) has reported the value of cervical sympathectomy both in the prevention and in the treatment of this condition. He attributes its value to increased transudation of fluid through the conjunctival capillaries. More than one factor may contribute to keratitis; Rowbotham (1939) mentioned this complication in a patient who had undergone Sjöqvist's operation of medullary tractotomy in which the corneal reflex was preserved; on the other hand, keratitis is a principal feature of Sjögren's disease in which there is xerophthalmia without neural involvement. (The diagnosis of Sjögren's disease, kerato-conjunctivitis, was in fact made when our patient, Case 15, was first seen in an ophthalmic clinic.) In view of the frequency of lesions of herpes simplex following operations on the trigeminus at any level, it is perhaps surprising that this virus has not been incriminated as the causal agent of keratitis; but so far no such evidence has been forthcoming. Indeed its lesions are rarely seen in the territory of the ophthalmic nerve. Braley (1952) stated that although over half the population will develop herpes of the lip after artificial fever therapy, only one in a thousand will have herpes corneæ.

Vasomotor and other lesions attributable to disturbance of autonomic nerves have been reported only after injection of alcohol into the Gasserian ganglion or after electro-coagulation. The classic paper by List and Peet (1938) is usually quoted as evidence that sympathetic fibres are not found in relation to the intracranial course of the trigeminus. Jefferson was reported by Rowbotham (1939) to have observed dilatation of conjunctival vessels, blushing of the eyelids and a small rise of local skin temperature during the injection of alcohol. He attributed this to diffusion of alcohol to the fibres of the carotid plexus. Harris (1935) described a similar experience while carrying out a second injection of the ganglion in his Case III. The vasomotor and related lesions which have been described include erythema, dryness and atrophy of the skin, alopecia and neurodermatitis. Examples of these changes are to be found in the reports of Howell (1955), Stühmer (1952) Mixter (1940), Loveman (1933), Netherton (1933), and Becker (1925). The role of dysæsthesiæ in producing the neurodermatitic lesions is unknown, but they are a common complication of all trigeminal operations. (Wilson, 1927; Rowbotham, 1939; Schorstein, 1943; Peet and Schneider, 1952; Penman, 1954).

A trophic disorder probably related in some way to autonomic dys-

function is the syndrome of facial hemiatrophy. It has been described as a consequence of trigeminal neuralgia of long duration: fifteen years and seven years in the cases of Surat (1930); and Brain (1955) in his textbook refers to 2 cases in which the changes of interstitial neuritis have been observed in the trigeminal nerve of the affected side. We know of no report of this syndrome following trigeminal sensory root section or similar operation.

The rarest complication, of which we are aware, of surgical denervation of the skin of the face is the "ulcération en arc" of the ala nasi, described in 1933 by McKenzie and by Loveman and rediscovered and reported with illustrations in 1949 by Jaeger at the 31st Congress of the Société Suisse de Dermatologie et de Vénéréologie (Jaeger, 1950). The largest series of such cases was reported in 1943 by Schorstein: 5 of his patients developed ulceration of the nose following injection of alcohol, 2 following root section, and 1 after an operation for removal of an acoustic neurinoma. This last case was illustrated with photographs showing progressive increase in size of the erosion between seven and fifteen months after the operation. The frequency of this lesion is unknown. McKenzie (1933) in following up 119 patients by post received replies from 78, of whom two had ulceration of the nose. His third case with ulceration was a patient in whom the trigeminal nerve had been sectioned during removal of an acoustic neurinoma. In Peet and Schneider's study (1952) of 689 cases of trigeminal neuralgia, they were able to follow up, by post, 338 patients who had had root section and they received reports from relatives on a further 44 who had died. In none of these was mention made of ulceration of the nose. But among 199 patients who had had previous injections of alcohol, they reported one who had a "slough and excoriation of the face with cartilaginous destruction after the procedure." The single cases reported by Loveman (1933), Tappeiner (1951) and Hodgson (1952) all followed injection of alcohol; Stühmer's case (1952) followed electrocoagulation. Harris (1940) had "occasionally" seen trophic lesions in 1943 cases treated by injection. 2 of the cases reported by Howell (1955) had had injections, and 1 had had root section. All 3 of Jaeger's patients (1950) had had sensory root section and Peet (1929, 1940) stated that he had had 3 cases of trophic lesion in 1,000 operations on the sensory root: 2 of these were in elderly patients who experienced intense dysæsthesiæ in a numb face and later developed ulceration of the ala nasi; the third had herpetic-like scars on the forehead when reviewed several years after operation. Knight (1954, 1957) reported 2 cases of ulceration of the ala nasi associated with herpes simplex. Our own illustration (fig. 4) is that of a 70-year-old man who developed ulceration of the right ala nasi twelve years after sensory root section. Trophic lesions, therefore, on the evidence of these reports, do not seem more likely to occur after any one of these several procedures. Dott (1951) has emphasized the use of

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cervical sympathectomy in promoting the healing of trophic ulcers of the nostril.

The literature contains some reports of ulcerative lesions of the face as a sequel to interruption of the trigeminal sensory pathways within the brain-stem. Karnosh and Scherb (1940) and Savitsky and Elpern (1948) have seen erosion of ala nasi and other changes in cases of medullary infarction due to thrombosis within the posterior inferior cerebellar artery and the former authors also record such lesions in a case of syringobulbia. The earliest report was that of Wallenberg himself (1901) who had first described the posterior inferior cerebellar syndrome in 1895, following a suggestion by Wernicke. His patient, a 55-year-old female, was seen to have "Excoriation am rechten Nasenflügel, Röthung der rechten Nasenhälfte" (Excoration of the right ala nasi, inflammation of the right side of the nose) which came on five months after her ictus. Rosenberg and Solovay (1939) had 2 cases in which the lesions were a complication of post-encephalitic parkinsonism. Trauma to the analgesic face is probably an important factor. Savitsky and Elpern suggested that in their patient, who had extensive, indolent erosion of the upper lip and ala nasi, the precipitating cause was the rubber gastric tube used for feeding during the acute stage of the illness.

Trophic lesions of the skin are commonly seen in leprosy. Erosion of the nose may result from ulceration of a cutaneous nodule or from leprous trigeminal neuritis. An example of the latter is shown in fig. 5; the typical "ulcération en arc" had developed in the anæsthetic trigeminal field of a leprous Jamaican.

Ulceration of the palate is stated to occur in tabetics as a trophic manifestation (Purves-Stewart, 1952; Darier, 1937). We have not seen reports of ulceration of the ala nasi in this disease nor in diabetes mellitus.

Monoplegia Masticatoria

Our single patient (Case 16) with involvement of both motor and sensory functions of the left trigeminus (fig. 6) was clearly different in kind from the other cases of the series. His initial symptoms which were sensory extended rapidly throughout the territory of the second and third divisions on the left, and within a week he was aware of impairment of taste and of muscular weakness on the same side. Actual muscle wasting, with falling in of his features, was soon evident and on opening his jaw it deviated to the left. The muscles were at first electrically inert, both to galvanic and faradic currents. When he was admitted to hospital seven weeks after the onset the process had already reached its peak and improvement had begun when he left hospital three weeks later. Recovery thereafter was tedious but was complete within a year.

The evolution of this illness suggested a virus infection: he had no signs of herpes zoster, the extensive sensory loss precluded a diagnosis of

poliomyelitis, and the solitariness of the lesion together with the normal content of protein in the cerebrospinal fluid made Guillain-Barré syndrome improbable. There were no signs of an acute systemic disorder.

Few cases of this kind have been published. Krabbe (1920) described a case which he had seen during the influenza pandemic of 1918–9. His patient was a 17-year-old student who had had a sore throat in January 1919 at a time when he was exposed to many cases of influenza and who had in fact been diagnosed as having this disease. Within a few days he had difficulty in opening his mouth and in chewing and this was followed by wasting of the side of his face. When he was seen by Krabbe nine months later, wasting of the right masseter and temporalis muscles was present, his jaw deviated to the right on opening, but the only sign of sensory disturbance was sluggishness of the right corneal reflex. Taste was unaffected. On the basis of the story Krabbe thought that influenza might have been the cause of the illness. Several cases of cranial neuropathy including trigeminal paresis were reported from Mannheim following the 1918 pandemic in Germany (Kaufmann, 1919). Münzer (1931) had a case of trigeminal motor paralysis without sensory loss arising in the course of an acute infection. The paralysis had almost recovered at follow-up eight months later. This patient's illness began with sore throat; enlargement of the spleen and an 11 per cent monocytosis in his peripheral blood were later findings. These suggest to us that the diagnosis may have been that of infectious mononucleosis. Möller (1956) reviewing 90 cases of brain-stem encephalitis and epidemic vertigo which he had seen at Sollefteå in Sweden between November 1948 and December 1954 referred to 5 cases of paresis of the fifth nerve; in 2 cases this was an isolated lesion and in 3 others it was combined with paresis of one or more cranial nerves. It is not clear whether the motor root was involved in these cases. In 2 the spread of sensory change followed the anatomical boundaries of the peripheral divisions but in 3 he considered that the distribution of the sensory loss was of the "onion-peel" type. In discussing acute neuritis of cranial nerves, Winther (1956) mentioned that he had seen 14 cases of "acute neuritis of the trigeminus" mostly in young women with an excellent prognosis of recovery within weeks or months.

Hill (1954) described 2 male patients in whom the onset was indolent. In 1 of these paræsthesiæ had spread over the right side of the face in the course of three months. He was examined at that time and was found to have weakness of masseter and pterygoid muscles with sensory loss in all three divisions and hemiageusia. The condition was stationary four years later. The second had weakness of mandibular muscles within a week of onset of paræsthesiæ on the left side together with third division anæsthesia and loss of taste; the signs in this case were also present after a four-year interval. In the same communication Rowland Hill stated that he had seen 12 such cases in recent years, slowly progressive at the start, some-

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times remitting partially, but usually leaving behind sensory, motor and autonomic palsies. He had frequently found a Horner's syndrome: slight ptosis was present in our patient (Case 16).

Localization and Pathogenesis

The site and nature of the lesion causing the syndrome which has been described in these cases await final demonstration by biopsy and pathological examination. But we consider that the localization and pathology of the process may be inferred from the clinical evidence. In the first place we are apparently dealing with a benign lesion of one or of both trigeminal nerves. No other part of the nervous system is involved and the general health of the patient is unaffected. Characteristically the modalities of pain, light touch and temperature discrimination are impaired whereas those arising from stimulation of deeper structures are not involved. The motor function of the trigeminus was interrupted only in one case which we considered to belong to a separate syndrome (monoplegia masticatoria).

The bifurcation of sensory fibres on entering the pons, those carrying tactile impulses being delivered to the main sensory nucleus, and those bearing painful and thermal stimuli passing in the descending root to the spinal nucleus, enable accurate localization of ponto-medullary lesions involving trigeminal pathways to be made. The very lack of dissociation of this kind in our cases excludes a primary disturbance within the brainstem. The disorder, therefore, is of the primary sensory neurones, at their peripheral origin, in the Gasserian ganglion, or in the sensory root up to the point of its division within the pons. With the exception of Case 15, which was in many respects atypical, autonomic involvement was inconspicuous. On the other hand the sense of taste was impaired in 7 cases out of a total of 13 in which the mandibular division was involved. Evidence has been quoted for supposing that, in cases of trigeminal paresis, ageusia is due to cortical imperception when the pathways of taste remain intact. Knowledge that sensory root section will cause ageusia in the majority does not exclude a peripheral lesion involving the chorda tympani where it is contiguous with the mandibular nerve; but it has then to be determined why the chorda tympani escaped in the remaining 6 cases (in 2 of them the mandibular division was affected on both sides).

We have, therefore, concluded from these clinical findings that the lesion is primarily of the intracranial path of the first sensory neurones, that is of the sensory root, Gasserian ganglion and proximal parts of the three principal divisions. Although we lack exact pathological support we have found some confirmation of our hypothesis in operative reports. Brodie Hughes (1958) published a short account of 3 cases of "Chronic benign trigeminal paresis" on each of which he had operated. The findings were of great interest. In each he found that "the sensory root

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appeared to be reduced to a few wisps of nerve fibre." There was a local arachnoiditis, and histological studies suggested that the lesion was a mild chronic inflammatory process, leaving the motor root intact. The onset of symptoms was acute and painful; within a few weeks his first patient, a male, experienced numbness in the cheek which spread gradually over a period of twelve years to involve the whole trigeminal territory. The story of the second patient, a female, was identical, extending over six years. The third patient, also a female, had a shorter history of only eleven months and her complaint was more of paræsthesiæ than of pain. He had also had under observation for four and nine years respectively 2 further cases of trigeminal sensory paresis whose symptoms had come on rapidly. Both were women. In all 5 cases there was impairment of touch and pain over most of the trigeminal area, densest in the region where symptoms had begun. Motor involvement was absent in all cases, and no evidence was found of autonomic dysfunction. Mr. Norman Whalley has allowed us to quote a case under his care in whom at operation he found that "root, ganglion and first and second divisions appeared grey and pink in colour, not the normal white appearance." No tumour nor other lesion was found, exposure of all structures being excellent. Mr. Whalley made a provisional diagnosis of "intrinsic neuritis" on these findings. Four months before operation this patient, a 36-year-old male, had noticed numbness of the right side of his face which came on rapidly and persisted with little alteration. The numbness involved the right side of his forehead, both upper and lower lips on the right, the inside of the cheek and the right half of the tongue. Taste was unaffected. Objective sensory loss was confined to the first and second divisions: the right corneal reflex was absent. He was last examined in April 1958, eighteen months after operation at which time his symptoms were less and the sensory loss had decreased. One of our own patients (Case 6) was operated on by Mr. Charles Langmaid; he reported that the ganglion did not appear to "be enlarged by tumour or involved in any inflammatory process." It seems to us possible that these surgical reports indicate three stages of a single process. Mr. Whalley's patient was operated on within four months of the onset of his symptoms; our own after three years; and the three patients of Brodie Hughes after twelve years, six years and eleven months. Tissue removed at the time of sensory root section in Brodie Hughes' cases showed degenerative changes in the remaining fibres. Satellitosis of ganglion cells was present together with collections of lymphocytes and an increase of fibrous tissue which showed hyaline change.

Too much importance should not be attached to degenerative changes in the Gasserian ganglion. In 1930 Opalski described the normal and pathological anatomy of the ganglion as the result of a study of 52 cases about which he appended brief clinical notes. None had had any particular complaint referable to the trigeminal nerves: the majority had died

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in a mental institution. As examples of the cause of death, he gave progressive paralysis in 9, arteriosclerosis in 17, senile dementia in 6; 1 had died of heart failure, another of tuberculosis. He found pathological changes in the Gasserian ganglia of most cases, but not of all, and stated categorically that the changes were not specific for any particular systemic disease. The changes were fully illustrated with 32 figures: they included gross distension of ganglion cells with other irritative phenomena; mixed lymphocyte and plasmacyte infiltration; proliferation and hypertrophy of capsule cells; and increase of fibrous tissue. He commented on the lack of sclerotic changes in the blood vessels. Cell outfall from ischæmia or from actual hæmorrhage was rare or non-existent and there were no cystic changes. In 2 cases he found granulomata.

These histological changes in cases without known trigeminal symptomatology in life do not invalidate the operative findings which we have quoted in support of our concept of trigeminal neuropathy. They serve only to underline the need for critical care in interpreting microscopical findings in nervous tissue suspected of abnormal function in life.

Differential Diagnosis and Conclusions

A true trigeminal sensory neuropathy, if such can be shown to have clinical and pathological substance, must be differentiated from a variety of disorders which may encroach on the sensory pathways from the face.

Personal enquiries suggest that cases of similar neuropathy are seen from time to time in neurological clinics in this country more frequently than the scant reference to them in the literature would suggest. It is possible that many of them are followed and investigated as cases of suspected tumour, the negative findings on lumbar puncture and radiological investigation leading to a "negative" diagnosis. Tumour of the Gasserian ganglion or of the sensory root, or the very rare neurinoma of a peripheral division, of which an example arising in the mandibular nerve was described by Cuneo and Rand in 1952, and other tumours beginning in or near Meckel's cave, constitute one of the most important differential diagnoses of trigeminal pain and sensory disturbance. To describe the dense sensory loss which he has found to be characteristic of malignant Gasserian invasion, Jefferson (1953, 1955) has coined the term "stone numb face." The proximity of the third division to Rosenmüller's fossa and to the lateral wall of the pharynx leads often to early involvement of this division. Pain is prominent in malignant invasion whether this is due to local spread of a nasopharyngeal carcinoma or to metastasis from a distant primary; and pain which often masquerades as classical trigeminal tic is a feature of meningioma arising from the dura of the cave of Meckel or its immediate vicinity and of the less common cholesteatoma or "pearly tumour" described by Dandy (1932) and by Olivecrona (1949).

In 3 of Olivecrona's 7 cases, neuralgia of the third division had been

present for seven years, six years and four years without abnormal signs; in the fourth, similar mandibular pain had occurred for a year and the homolateral corneal reflex was sluggish. The relative youth of these 4 patients, whose average age was approximately 27 years, led to suspicion of tumour. The remaining 3 cases presented with signs which immediately carried them beyond differential consideration of trigeminal neuropathy.

The diagnosis of trigeminal neurinoma is even more difficult. Jefferson (1955) has said that some change in the sensibility of the face is commoner, early on, than severe pain and enumerated such symptoms as stiff feelings, pins and needles, and worrying numbness. The sensory loss on examination is not so striking as the patient's description would suggest. Other cases presented with atypical facial pain and characteristically had an absent corneal reflex; a few had facial hyperæsthesia. In his series of 7 cases, involvement of the motor root was uncommon and was found in 2 cases only. An equally confusing picture of the early symptomatology of these tumours was presented by Olive and Svien (1957). They had 13 cases and referred to 43 cases which they had been able to find in the literature; the neurinoma of the trigeminus is a rare tumour. In the majority of their 13 cases symptoms began in middle life, starting over the age of 30 in 11, and over 40 in 5. They classified them in three groups; supratentorial, infratentorial and mixed presentation. All cases in which tumour tissue lay beneath the tentorium had signs of a posterior fossa lesion; 4 of their 6 cases in which the tumour was supratentorial had objective signs of involvement of the motor root. A fifth case presented with exophthalmos and had extensive radiological signs; the sixth case was a finding at autopsy in a patient who had died of Hodgkin's disease and in whom there had been no trigeminal symptoms in life. 4 of their cases with extension to the posterior fossa also had weakness of masticatory muscles, but in 1 of them this was due to hypoglossal involvement. The finding of motor trigeminal impairment in at least 7 cases is in striking contrast to Jefferson's report. A compressing lesion might be expected to disturb motor and proprioceptive function before affecting the superficial sensory modalities which are carried by the smaller and more resistant fibres. Jefferson's observation, therefore, is particularly significant. In 2 of the cases described by Olive and Svien and in 1 of Jefferson's no objective trigeminal signs were found; the former authors also reported the case of a youth of 17 years whose symptoms of left trigeminal neurinoma began with bouts of involuntary laughter. This case has now been described in detail by Wood, Svien and Daly (1958). In 5 of Jefferson's cases the protein content of the cerebrospinal fluid was increased; similar increase was found in the 2 cases of Olive and Svien in which this examination was made. Jefferson stressed the value of basal radiographs of the skull in which enlargement of the exit foramina of the lower trigeminal divisions might be detected.

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Other possible causes of trigeminal paresis include exposure to toxic drugs such as stilbamidine and trilene, syphilis, inflammations, infiltrations and metabolic degenerations such as have been described in association with zoster, leprosy, Guillain-Barré syndrome, diabetes, sarcoidosis and primary amyloidosis. The Wassermann reaction was negative in all our cases and none had been exposed to any drug known to affect the trigeminal nerve. One of our patients was diabetic but her trigeminal disorder had preceded symptoms of diabetes by two years and records of many urine tests which were negative for sugar were available from an earlier hospital admission for an unrelated disorder. No patient had had a rash suggestive of zoster and none had had recurrent attacks of herpes simplex or of ulceration of the mouth as occurs in Behçet's disease. Leprosy and Guillain-Barré syndrome were excluded on the clinical findings, although it may be pertinent to recall Guillain's description in 1937 of residual trigeminal hypæsthesia following the cranial form of Guillain-Barré syndrome. Daly, Love and Dockerty (1957) have recorded a case of primary amyloid tumour of the Gasserian ganglion: trigeminal pain and paræsthesiæ were the presenting symptoms in their patient in whom second and third division sensory loss was present together with a sluggish corneal reflex, electromyographic but not clinical signs of motor involvement and decalcification of the middle fossa on radiography. The history of trigeminal numbness had begun *eleven years* previously. It is unlikely that the radiological signs were present at that time, so that clinical differentiation from trigeminal sensory neuropathy would have been impossible. Similarly differentiation from an isolated lesion of sarcoidosis may be impossible for, as Michael Jefferson (1957) has pointed out, this disorder may be present in the nervous system without any of its systemic manifestations. He found that most of the cranial nerves could be involved singly or in any combination, though often transiently. 1 of his 7 cases had sensory impairment in the field of the right trigeminus as part of the neurological picture. In a review of 115 cases from the literature Colover (1948) found a similar trigeminal lesion in 5 cases of sarcoidosis of the nervous system. The case described by Stammers (1930) of a 44-year-old woman with a history, over four months, of trigeminal paræsthesiæ and anæsthesia and with external rectus palsy—his Case 8—in whom at operation the Gasserian ganglion was found to have been replaced by non-caseating granuloma, might be an example of sarcoidosis.

Lesions within the brain-stem of a size to involve both tactile as well as pain and thermal pathways of the trigeminus would necessarily give rise to other symptoms and signs which were absent in our cases. Geréb (1948), however, described a case of presumed thrombosis of Duret's trigeminal artery which caused dense sensory loss around the angle of the mouth and lower lip and, to a lesser degree, of half of the tongue, inside of the cheek,

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gums and palate. Taste was also lost on the same side. The onset was sudden and the patient, a woman aged 36 years, had transient vertigo, vomiting and ataxia. It is possible that thrombosis of such a small vessel could give rise to the trigeminal signs without causing a cerebellar syndrome. Other vascular causes of the syndrome which we are describing might be intracranial aneurysm and the mononeuritis of polyarteritis nodosa, but in our experience aneurysm does not present in this fashion and there were no grounds for diagnosing a generalized vascular disease.

In the monograph by Wartenberg (1958) on "Neuritis, Sensory Neuritis and Neuralgia," 7 cases were described of trigeminal sensory paresis. 2 of his cases had bilateral involvement: a female, aged 28, had sudden onset of right facial numbness which was followed by similar symptoms on the left side four months later (page 185); a 50-year-old male had a year's history of soreness and numbness of the left side of his face, with similar symptoms developing on the right side three months later (page 199). Sensory loss in the second and third divisions on both sides of the face was confirmed in these 2 cases but there was no report of follow-up. Another case without adequate follow-up was a female, aged 25, who had sudden numbness on one side of her face and in whom hypalgesia and hypæsthesia were present in all three divisions (page 198). Similar to this case was another female, aged 50, in whom numbness of the face was preceded by burning paræsthesiæ, symptoms beginning six months before examination at which anæsthesia of the third division only was found (page 197). 3 patients had a more protracted history: all were females, aged 58, 30 and 47. The first of these had burning sensations in the left side of her face and tongue, followed by numbness, with objective signs in second and third divisions. Her signs were unaltered six years later. The second of these cases had sudden right-sided numbness after a respiratory infection, and anæsthesia of second and third divisions was still present at follow-up, fifteen months after the initial examination. The last case was a woman aged 47 who had had left facial paræsthesiæ for seven years: analgesia without anæsthesia was found in the whole left trigeminal territory and was unchanged after two years' observation. (These 3 cases were reported on pages 197 and 198 of the monograph.)

Wilfred Harris in a series of communications has drawn attention to the trigeminal presentation of disseminated sclerosis (1935, 1940, 1950, 1952). The latest figures which he has published (1952) showed that out of a total of 2,083 cases of trigeminal neuralgia 3·1 per cent were also diagnosed as having disseminated sclerosis. In an earlier report (1927) he had stated that *bilateral* tic was relatively more common in cases who also had sclerosis.

The commonest syndrome of which in 1950 he had seen 64 examples was trigeminal tic occurring in a known case of disseminated sclerosis: the spinal disease usually occurred before the trigeminal, but occasionally the order

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was reversed. None of these cases had had antecedent trigeminal numbness. Sometimes numbness and anæsthesia with hemiageusia occurred in cases of disseminated sclerosis but trigeminal tic did not follow the sensory loss. Three examples of this combination were given in his 1935 paper. The third of these had had transient facial numbness with contralateral thermanæsthesia of the lower limb sixteen years before florid signs of disseminated sclerosis appeared. Harris considered this syndrome typical of cases with a pontine plaque. In 1950 he described a case of trigeminal neuritis in whom signs of disseminated sclerosis developed after nineteen years. This patient had sudden numbness of the whole of one side of her face with hemiageusia which improved after a year. Seven years later, when she was aged 28, she began to experience severe pains in the same side of her face which continued until Gasserian ganglion injection was carried out by Harris after nearly twenty years. At that time she had been ataxic with disturbed control of her bladder for six or seven years. Eight years later she was unable to get about but was free of pain.

In 1928 Parker had published a report on 4 cases of disseminated sclerosis with trigeminal neuralgia. He described the autopsy findings of a case in which a plaque had been demonstrated in the sensory root at the lateral border of the pons. Typical left-sided neuralgic pain had occurred for six years without demonstrable trigeminal anæsthesia. Sensory root section was performed, the patient dying four days later of acute dilatation of the stomach. The main sensory nucleus and part of the spinal descending root of the *right* trigeminus were involved in the sclerotic process although no symptoms or signs had been present in life in the right trigeminal field. The *left* root was engulfed by two plaques as it emerged from the pons, the process extending a short distance along its extrapontine course but ending well short of the point of surgical division.

This finding was quoted by Harris (1935) when he reported 3 cases of "Paroxysmal neuralgic tic as a sequel to trigeminal neuritis." These patients had total unilateral facial analgesia which was so dense that the cheek was bitten unawares. The numbness lasted from a few weeks to four years and was followed, as remission began, by paroxysmal trigeminal pain. Harris injected the Gasserian ganglion with alcohol, in each case with complete and sustained relief of pain, and followed them up over many years. In 1950 he reported that his first case had died at the age of 81, some sixteen years after the injection, with no signs other than those of trigeminal anæsthesia and hemiageusia. His second case whose numbness had lasted four years, then to be followed by trigeminal pain, was alive and well eighteen years later. Her brother, a doctor, had reported that there were no signs of disseminated sclerosis. The third case was lost sight of after four years when he was already 80 years old. At that time he was well without signs other than facial numb-

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ness. To these 3 cases, Harris (1950) added a fourth, a female with signs of disseminated sclerosis which had begun nineteen years after her initial trigeminal numbness—this case has already been discussed above—and a fifth, a woman aged 62 who had had an episode of left trigeminal numbness lasting six weeks when she was 50. A year later she had a short-lived bout of third division pain which remitted for eleven years. She was injected by Harris when this pain recurred and was without further symptoms five years after this procedure.

Harris was careful to point out that, although the paroxysmal pain, its character, duration and anatomical distribution were all similar to trigeminal tic, it differed from the idiopathic disease in the absence of "triggers." Elsewhere he had advanced the hypothesis that the source of pain in trigeminal neuralgia was peripheral, in the jaw and teeth. In support of this he referred to the site of the pain, the absence of trigeminal sensory loss and to its frequent occurrence after injuries to the jaws. Moreover, the pain of neuralgia was relieved by operations on the sensory root whereas section distal to the lesion, as in cases of pain due to tumour and medullary thrombosis, gave no relief. Returning to Parker's demonstration of a plaque of sclerosis in the sensory root, Harris suggested that his 6 cases of trigeminal neuritis, described in 1935 and 1950 and his 3 cases of disseminated sclerosis with an episode of trigeminal numbness, illustrated two pathological sequences: trigeminal numbness and ageusia followed by tic; and trigeminal numbness and ageusia followed (or preceded) by disseminated sclerosis but without subsequent tic. This suggested to him that a lesion of the sensory root was the common denominator of the two conditions: a plaque of sclerosis in the cases of frank disseminated sclerosis, an area of "neuritis" in the others. As recovery of function occurred, peripheral stimuli could cause paroxysms of pain by stimulating fibres in a state of heightened "irritability." Some recovery of sensory function would have to occur before peripheral stimuli reached the involved segment and this was matched clinically by remission of numbness before the onset of painful paroxysms. The neural lesion which he postulated, and which had been demonstrated in Parker's case, seemed to him analogous to the lesion of retrobulbar neuritis.

Although Harris' cases differ in some respects from our own, these differences seem to us to be of degree and not of kind. The sequence in his patients was numbness followed after a varying interval by trigeminal pain as the numbness subsided. Pain was the initial symptom in 7 of our cases and was itself displaced by numbness and paræsthesiæ: in one case it was severe enough to warrant sensory root section. In our other cases numbness tended to come on insidiously and was only sometimes accompanied by uncomfortable paræsthesiæ or by actual pain. Similar variations in presentation were reported by Wartenberg (1958) and by Brodie Hughes

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(1958); and analogous symptoms have often been reported following sensory rhizotomy or Gasserian injection, and after stilbamidine therapy (Smith and Miller, 1955) in patients with trigeminal neuralgia. The degree and extent of pain and paræsthesiæ differ in every case of "neuritis," whatever the ætiology may be: in none is this variability more striking than in herpes zoster. The autopsy findings described by Denny-Brown and his colleagues (1944) in a case of zoster are pertinent to the present discussion. They found a cervical ganglionitis and irregular facial neuritis from infection with the virus, a series of lesions not dissimilar to those we have postulated in our cases. (Curiously, one of our patients—Case 6—had previously had a Bell's palsy as had one of the patients reported by Brodie Hughes.) There was no sign of zoster infection in any, nor was there a story of recurrent attacks of herpes simplex. Over the years, studies have pointed to a peculiar relation between this virus and the fifth nerve, which have been reviewed and amplified by Carton and Kilbourne (1952) and by Behrman and Knight (1954, 1956; and Knight, 1957). Braley (1952) in his Gifford Lecture examined the clinical presentation of herpes corneæ. This may range from an acute illness of a fortnight's duration to a chronic lesion, keratitis metaherpetica; each syndrome being accompanied by its own pattern of immunological response. A similar pattern of responses between virus and neural cell can be imagined: herpes or a related virus might be the causative agent in some of our cases.

Summary

(1) 16 cases of isolated trigeminal neuropathy are discussed. In 15, sensory function only of the nerve was disturbed.

(2) In one case both motor and sensory functions were impaired. This case was classified separately: a viral ætiology was considered. Similar cases have been reported in the literature under the title of "monoplegia masticatoria."

(3) The clinical features of the 15 cases of chronic trigeminal sensory paresis are described. The course of the disorder tends to be indolent and benign. Taste may be involved, and sometimes autonomic fibres. In one case there was trophic destruction of the nose, bilateral xerophthalmia and xerostomia.

(4) The differential diagnosis has to be made from tumours and from inflammation, infiltration and degeneration of the Gasserian ganglion.

(5) Similar cases which have been described in the literature are reviewed, particularly those germane to questions of ætiology.

Acknowledgments

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FIG. 1A and B (*Case* 15).—1951: Erosion of left ala nasi. Bilateral corneal scars, ptosis and xerophthalmia.

FIG. 2A and B (*Case* 15).—1957: Total destruction of nose.

To illustrate article by John D. Spillane and C. E. C. Wells.

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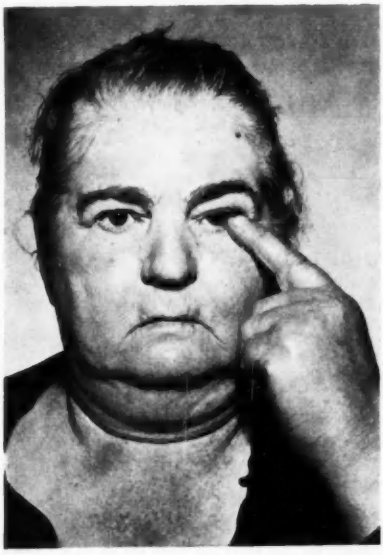

FIG. 3 (*Case* 6).—Left Horner's syndrome and anæsthetic left cornea.

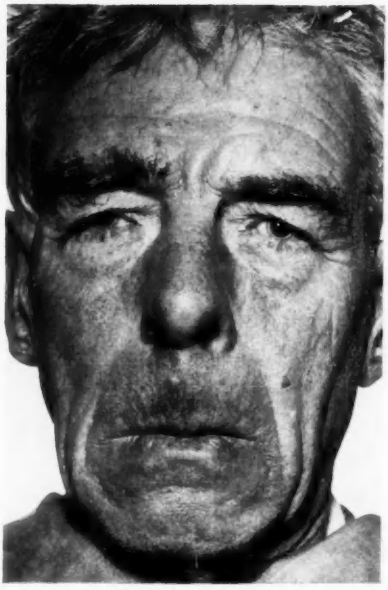

FIG. 4.—Erosion of the right ala nasi in a 70-year-old man which began twelve years after right trigeminal sensory rhizotomy for trigeminal neuralgia.

FIG. 5.—Erosion of the left ala nasi in a Jamaican woman with leprous trigeminal neuritis.

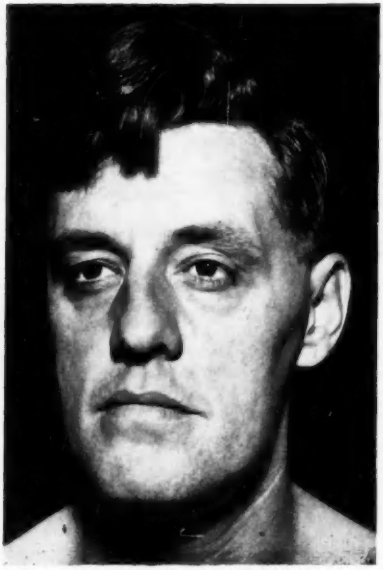

FIG. 6. (*Case* 16).—Left ptosis; wasting of left masseter and temporalis muscles.

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PREGNANCY AS A FACTOR INFLUENCING RELAPSE IN DISSEMINATED SCLEROSIS

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INTRODUCTION

THE possible association between pregnancy and relapse in women suffering from disseminated sclerosis has been frequently discussed. Earlier in this century German physicians stressed the adverse effect of pregnancy and labour on the course of the disease (von Hoesslin, 1904, and 1934; Beck, 1913; Gobermann, 1927; Dimitz, 1928, and Fleck, 1938), but more recent statistical studies have failed to support earlier opinions (Müller, 1949; Tillman, 1950, and McAlpine, Compston and Lumsden, 1955).

Theoretically the hypothesis, that pregnancy increases the risk of relapse, can only be tested adequately by exacting prospective study. This would entail continued observation of a large number of women from onset of their disease to the end of reproductive life, and accurate documentation of all pregnancies and relapses experienced. With such data relapse rates of women who had pregnancies and those who had none could be compared, and relationships in time between pregnancy and relapse could be studied. Even so, corrections would be required to ensure that comparisons were not invalidated by factors, unrelated to pregnancy but influencing relapse rates, which might be differently represented in the otherwise comparable groups. Though desirable, a prospective study would also involve much time and labour because of the length of the human reproductive period and the relatively low frequency of the disease. There have been no such studies and retrospective data are few. So, on account of the clinical implications of a possible association between pregnancy and relapse, we have used the information obtained by two of us in a survey of Northern Ireland to see if anything can be added to present knowledge on the subject.

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Data

The original case records compiled by Allison and Millar (1954) for all persons found to have disseminated sclerosis in Northern Ireland, included information about sex, marital condition, age and date of onset, dates of relapses and pregnancies and age and date when last seen. A diagnosis of disseminated sclerosis was made in 390 women and in what follows we have used the records of 262 of these. The 128 omissions were unavoidable. In 35 the onset had been after the age of 45 years, and this age, as will be seen later had been accepted as the end of the reproductive period. The records of the remaining 93 omitted cases were considered unreliable; they included 25 in which there were no relevant details about onset, 22 with onsets outside Northern Ireland and 46 with doubtful details about relapses.

We define a relapse as the appearance of symptoms occurring at a clear interval after the onset of the disease. This would include any exacerbation of previous symptoms lasting longer than a few days.

Examination of Data

The period during which a patient was at risk of relapse was estimated by counting the number of years from onset of symptoms to age 45 years or date when last seen (whichever was earlier). This resulted in a total exposure experienced by the 262 women of 3,509 years. During these years three hundred and sixty-five relapses had occurred, resulting in a relapse rate of 0·104 relapses per woman per year. Table I shows that the rates for single and married women were identical.

Table I.—Preliminary Examination of Data

	Single women	*Married women*
Number of women	111	151
Total years of exposure*	1,580	1,929
Number of women who had one or more relapses	77	102
Total number of relapses	164	201
Relapse rate per woman per year	0·104	0·104
Number of women who had one or more pregnancies after onset		70
Total number of pregnancies after onset (i.e. number of pregnancy years†)		170
Number of women who had one or more associated‡ relapses		33
Number of associated‡ relapses		45
Relapse rate per pregnancy year†		0·265

*Each woman's exposure estimated from onset to age 45 or age last seen if before 45 years.

†Pregnancy year = 9 months of pregnancy plus 3 months after pregnancy.

‡"Associated relapse"=relapse in pregnancy year (six associated relapses occurred in pregnancy and thirty-nine in three months after pregnancy).

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If a "pregnancy year" is defined as the nine months of pregnancy and the three months following pregnancy, then the total period of exposure included 170 pregnancy years in which forty-five relapses occurred, resulting in an average relapse rate of 0·265 relapses per pregnancy year. This rate is more than double the average (0·104 relapses per year) for single or married women. Such a difference is most unlikely to have arisen by chance ($P<0·01$).

Further, if a relapse in a pregnancy year is defined as an "associated" relapse, then by chance three-quarters (33·75) of the forty-five associated relapses might reasonably be expected to have occurred during a pregnancy and one-quarter (11·25) during the remainder of a pregnancy year (i.e. in a puerperium). In fact, only six associated relapses occurred during pregnancies and as many as thirty-nine in puerperia—a difference from expectation most unlikely to be attributable to chance ($P<0·01$).

These findings suggest that the relapse rate experienced immediately after childbirth is, on average, higher than that experienced at other times, either by single or married women. They raise the possibility of a causal association between childbirth and relapse, but further analysis is necessary because there are several other possible explanations of the observed association that must be taken into account.

Method of Analysis of Data

It has been suggested that relapse rates in disseminated sclerosis vary, among other factors, with age of onset of the disease and with its duration. In Table II the relapse rates are shown for all 262 women in this series combined; they suggest that the risk of relapse is high in the period 1–5 years after onset as compared with later quinquennia, although no obvious effect of age of onset on relapse rates is apparent.

Later it will be necessary to make comparisons of relapse rates between

Table II.—Relapse Rates per Woman per Year Based on Data for Single and Married Women Combined Classified by Age at Onset and Year after Onset in which Relapse Occurred

	Age of onset in years						
Years after onset	*Less than* 15	15–19	20–24	25–29	30–34	35–39	40–44
0–	—	0·03	—	0·04	0·07	0·09	0·04
1–5	0·23	0·12	0·16	0·14	0·15	0·16	0·10
6–10	0·07	0·08	0·11	0·09	0·12	0·08	
11–15	0·13	0·09	0·14	0·06	0·06		
16–20	0·05	0·10	0·10	0·06			
21–25	0·03	0·05	0·01				
26–30	0·05	0·14					
31–35	—						
36 and over	..						

—=nil. ..=no data.

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different groups of women for all or specified years of their illness. If the numbers were sufficient, this could best be done by preparing tables, like Table II, for each group and comparing the relapse rates in corresponding cells of the tables; in this way comparison of like age of onset and year after onset groups would prevent these two factors from influencing the comparison. However our numbers are too small for this procedure, and as a compromise, the rates of Table II have been used to obtain for any specified group of patients, or period of exposure, expected numbers of relapses for comparison with those observed in the group or period concerned. The procedure used for a given group of women was first to divide them into the age of onset groups of Table II. Then for each age of onset sub-group the total number of years' exposure in each of the "year after onset" groups of Table II was counted. Thus, a given group of women might have included, say, 20 with age of onset 15–19; all 20 women might have been exposed for the first year after onset (year 0). 18 of them might have been exposed in the second year (year 1); 16 in the third (year 2) and fourth (year 3) and 10 in the fifth and sixth giving seventy years of exposure in the 1–5 years after onset period. Similarly there may have been a total of fifty years of exposure in the 6–10 years after onset period; forty in the 11–15 years after onset period, etc. Now if these 20 women had experienced the average relapse rates for all women of the same age, as shown in Table II, then the expected number of relapses would have been $(20\times0{\cdot}03)=0{\cdot}6$, $(70\times0{\cdot}12)=8{\cdot}4$, $(50\times0{\cdot}08)=4{\cdot}0$, $(40\times0{\cdot}09)=3{\cdot}6$, etc., respectively in the periods after onset 0, 1–5, 6–10, 11–15 years, etc. If this calculation is repeated for each other age sub-group of the given group then the sum of all the expected numbers of relapses will represent the number of relapses which would have been experienced by that given group if the average rates for all 262 women at appropriate ages of onset and duration of disease had been experienced. Any difference between the number of relapses observed and expected cannot thus be due to women in the group considered having had a different distribution by age of onset, or having been exposed for a different duration of disease, from other women. Any such difference between observation and expectation can arise by chance or because the group considered differs from other women in some other quality which influences their relapse experience. The approximate probability of the difference occurring by chance is estimated and shown as P and conventionally $P<0{\cdot}05$ is taken as significant (i.e. the difference is unlikely to arise by chance).

Possible Explanations of Observed Association

(1) If pregnancies occurred mainly at a stage of the disease when the relapse rate was above average level (e.g. 1–5 years after onset), or if women who had pregnancies had their onset of disease at an age associated

with higher than average relapse rates, then relapse rates in pregnancy years could reasonably be expected also to be above average level. The association observed in Table I could support this, but the concentration of associated relapses in the puerperium would still require explanation.

However, all the relapse rates of Table II are lower than that observed in pregnancy years, and more explicitly the expected number of relapses in pregnancy years is 18·25 whereas forty-five were observed (Table III)—an unlikely chance difference ($P<0·01$)—so that it would appear that the excessive relapse rate in pregnancy years is not likely to be due to these pregnancies occurring at a year after onset, or to their occurring in women with an age of onset, usually associated with excessive relapse rates.

TABLE III.—OBSERVED AND EXPECTED* RELAPSES FOR DEFINED GROUPS OF WOMEN AND EXPOSURE PERIODS

Women considered	*Years of exposure considered*	*Observed (O) and expected (E) relapses*			*Approximate probability of (O-E) being exceeded by chance*
		O	*E*	*(O-E)*	
Single	All years	164	164·10	−0·10	>0·9
Married	All years	201	200·90	+0·10	>0·9
Total	All years	365	365		
Married, no pregnancies	All years	82	81·17	+0·83	>0·9
Married, one or more pregnancies	All years	119	119·72	−0·72	>0·9
All married	All years	201	200·90		
Married, one or more pregnancies	Pregnancy years	45	18·25	+26·75	<0·01
	Other years	74	101·47	−27·47	<0·01
	All years	119	119·72		
Married, one pregnancy only	Pregnancy years	14	3·55	+10·45	<0·01
	Other years	29	35·09	−6·09	0·3–0·5
	All years	43	38·64	4·36	0·3–0·5

*Expected numbers based on rates for all women in Table II (*see* text).

(2) It could be argued that women who had relapses at or about the time of some important event in their lives would be more likely to remember such relapses than women who had experienced no such simultaneous events to act as aids to memory. In this way an excess of relapses in pregnancy years might result from women remembering the double events of pregnancy and relapse rather than the single event of relapse alone. If this were true of these data it would be reasonable to expect women who had children to have higher relapse rates than others. Table I suggests that this is unlikely because the average relapse rates of single and married women were the same. However Table I

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could be misleading if single women had relatively more years of exposure than married in the early years of disease when relapse rates are high. The expected number of relapses for single and married women, as Table III shows, is remarkably similar to the number observed in each case. Moreover, Table III also shows that the agreement between observed and expected persists both for married women who had children and those who did not.

Consequently there is no evidence that the 170 pregnancies experienced by the 70 mothers enabled them to remember relapses better than other women. This being so, it follows that the excess of relapse rates in pregnancy years is likely to be balanced by a deficit in other years among women who had pregnancies.

(3) Patients who had relapses at or about the same time as pregnancies might tend in retrospect to associate the two events more closely in time than was, in fact, the case. This would result again in a balance of excess relapses in pregnancy years by a deficit in other years in the same women. This situation was foreshadowed in the previous paragraph and is now shown to be so in Table III. In years other than pregnancy years the 70 women who had pregnancies experienced seventy-four relapses against 101·47 expected—a difference unlikely to have arisen by chance ($P<0{\cdot}01$) and suggestive, among women who had at least one pregnancy after onset, of lower relapse rates in non-pregnancy years than in pregnancy years.

(4) However the same result could have arisen in a completely different way, if it were accepted that no tendency existed to relate pregnancies and relapses more closely in time than was actually the case. In favour of such a view is the fact that we are dealing only with independently confirmed records. On this assumption the balance of the excess of relapses in pregnancy years by a deficit in the same women in other years could arise because pregnancy or childbirth had altered the natural course of the disease.

Thus a relapse due to occur at a given point in time might be delayed by a pregnancy until after childbirth or brought forward, i.e. "anticipated" by the childbirth. It seems unlikely that a relapse due before a pregnancy began could be influenced so that the delaying process could operate only by postponing to the puerperium relapses due in the natural course during pregnancy. Such a postponement seems unlikely from our data because even if the associated relapses were randomly distributed over pregnancy years, the number of relapses during pregnancies would be 33·75 which is still significantly greater than the 18·25 expected in the whole of the pregnancy years on the basis of the rates of Table II.

Thus anticipation of relapse seems the more tenable of the two alternatives. This implies that about half of the associated relapses occurred in the three months following childbirth because the events

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of childbirth precipitated relapses, which would not have occurred naturally until later. If this is so, then the women who had associated relapses are more likely than other women who had pregnancies to have lower relapse rates in the years when they did not have pregnancies. This is, in fact, supported by the data. The 33 women who had the forty-five associated relapses also had twenty-six relapses in years other than pregnancy years, whereas 43·05 were expected on the basis of the rates for all women. This deficit is unlikely to have occurred by chance ($P<0{\cdot}01$). The 37 women who had pregnancies but did not have associated relapses, experienced forty-eight relapses in non-pregnancy years which, though less than the number expected (58·42) on the rates for all women, is not significantly less ($0{\cdot}20>P>0{\cdot}10$). It will be appreciated that much more data are required to resolve this argument. At present little more can be said than that these data show no inconsistence with the theory that when pregnancy occurs in a woman with disseminated sclerosis, in addition to the risk of relapse experienced by all women, there is an added risk that after childbirth she will anticipate a relapse which, had the pregnancy not occurred, she would probably have had later in the course of her illness.

(5) The average number of pregnancies per woman, who had at least one pregnancy, was 2·43, but there were some women who had many pregnancies so that associated relapses might result from the exceptional experience of a few women. When, however, the analysis is limited to women who had only one pregnancy then although the numbers are small the results are materially the same. Table III shows that fourteen associated relapses occurred in women who had only one pregnancy whereas only 3·55 were expected and this difference is unlikely to be explained by chance ($P<0{\cdot}01$). In other years the same women experienced twenty-nine relapses compared with 35·09 expected; thus in non-pregnancy years there was a deficit, although with the numbers involved it might easily have arisen by chance ($0{\cdot}50>P>0{\cdot}30$).

(6) It could be argued that relapse rates calculated on the basis of relapses per year of exposure are misleading if the duration of relapses often exceeds a year. Thus, for example, if a woman begins to relapse in one year and this continues over two years, she cannot be exposed to risk of relapse in the second year and should not be counted as such. It was impossible to make corrections for this possible error from the available records and we have had to assume that no relapse lasted for more than one year. Although remission after a year may be possible, in most cases it occurs within a year and the assumption therefore, so far as we can see, is reasonable.

(7) The overall differences and similarities between observed and expected numbers of Table III might hide subtle differences in relapse rates at specific years after onset or in women of specific ages of onset.

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As has been said, the method of analysis is a compromise because of the small numbers involved. In Table IV we have broken down the observed

TABLE IV.—OBSERVED (O) AND EXPECTED (E) RELAPSES OF TABLE III SUBDIVIDED BY YEAR AFTER ONSET IN WHICH RELAPSE OBSERVED OR EXPECTED AND BY AGE OF ONSET OF DISEASE OF WOMEN CONCERNED

Women considered	*Years of exposure considered*		*Age of onset in years and years after onset in brackets* <25 (0–5)	<25 (6+)	25+ (0–5)	25+ (6+)	*Total (see Table III*
Single	All years	O	52	54	38	20	164
		E	43·6	61·8	37·7	21·0	164·1
Married	All years	O	28	70	68	35	201
		E	36·4	62·3	68·3	34·0	200·9
Married, no pregnancies	All years	O	10	17	40	15	82
		E	9·5	11·9	43·6	16·1	81·2
Married, one or more pregnancies	All years	O	18	53	28	20	119
		E	26·9	50·4	24·6	17·9	119·7
Married, one or more pregnancies	Pregnancy years	O	7*	15*	12*	11*	45*
		E	3·0	8·0	4·6	2·6	18·2
	Other years	O	11*	38	16	9	74*
		E	23·9	42·4	20·0	15·3	101·5
Married, one pregnancy only	Pregnancy years	O	4	2	6	2	14*
		E	0·9	0·4	1·7	0·6	3·5
	Other years	O	5	10	11	3	29
		E	6·3	11·8	10·7	6·4	35·1

*Approximate probability of (O-E) being exceeded by chance is $P<0{\cdot}05$—this assessment has not been made when E is very small.

and expected relapses, for each category of Table III, into four sub-groups of age of onset and year after onset. The result of this breakdown provides no evidence of heterogenity although the sampling errors are unavoidably large in the small sub-groups and are bound to confuse the comparisons within them. As far as is possible to tell, this subdivision does not necessitate any modification of what has gone before.

DISCUSSION

Seven possible criticisms of the observed association between relapse and childbirth (Table I) have been considered with the result that two possible explanations of the phenomenon remain:

(1) Women who have pregnancies tend to date subsequent relapses closer to the childbirth than is, in fact, true.

(2) Women who have pregnancies experience the risks of relapse similar to other women, but in addition they experience, as a result of possibly one in every ten childbirths, anticipation of a relapse which would have occurred later in their illness.

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To these explanations must be added the possibility that the influence of some factor not considered by us, but which affects relapse rates, has had a greater effect in pregnancy years than in others. The presence or importance of such "unknowns" is only likely to be detected by a detailed study of relapse rates in this disease. Thus our data can give no information about duration of relapse and remission or severity of relapse and assumes that relapses are independent events.

We think that of the two explanations given above, the true anticipation effect is the more likely because independent confirmation of relapse dates is available in our data, even though dating the onset of a relapse is often difficult and the memory effect cannot be ruled out. Only prospective studies are likely to resolve this difficulty.

Müller (1949) compared the proportion of childbirths associated in pregnancy years, as defined above, with relapse "bouts" and the proportion of relapses in the number of patient-years exposure of all women. He subdivided his data by age of onset and duration of illness, but could find no evidence of any material difference in these proportions. His proportion of childbirths with associated relapses ranged from 14 to 22 per cent while his proportion of patient-years with relapses ranged from 17 to 29 per cent. Although his approach was different, if our findings had applied, the former percentages should have been the greater. Indeed his relapse rates for all women appear to be high compared with ours of Table II.

Tillmann (1950) analysed 19 cases from the Sloane Hospital in New York, a maternity hospital, and 278 cases from the Neurological Institute. He reported that of 52 women suffering from multiple sclerosis who had seventy pregnancies, 30 were unchanged, 4 had remissions, 6 had relapses and the disease was exacerbated in 22 during the puerperium. He concluded that pregnancy did not accelerate the disease and was not "significant" in its development. However, twenty-two exacerbations and six relapses might be interpreted as giving 0·40 relapses or exacerbations per pregnancy year. McAlpine *et al.* (1955) reported on thirty-three pregnancies in 24 patients; of these 9 relapsed in association with eleven pregnancies. Thus 33 per cent of these pregnancies were associated with relapse—a proportion not significantly different from ours ($0{\cdot}60 > P > 0{\cdot}50$). In their series it did not differ "significantly" from their general annual relapse rate of 39 per cent which was again much higher than ours which is equivalent to 10·4 per cent. Like us they found no difference in relapse rate between child-bearing and other women; their annual relapse rates were 42 and 48 per cent respectively. However, none of the comparisons with other work can be precisely assessed because of differences in age of onset and duration of disease in the various series.

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Conclusion

The data of Allison and Millar (1954) which have been used, reveal no evidence of an ultimately worse prognosis in terms of frequency of relapse for child-bearing women than for others. There is evidence that relapses which would have occurred to women who experience pregnancy are sometimes "anticipated" by the pregnancy although they would probably have occurred anyway at a later date. It is suggested that this "anticipation" might be brought about by the stresses of labour and increased work and responsibility of the puerperium since other stresses such as trauma, infection and emotional disturbances have elsewhere been implicated (McAlpine *et al.*, 1955). But this suggestion needs investigation preferably by prospective study, as it implies that any stress, "therapeutic" or otherwise provoking a relapse in this anticipatory fashion might be expected to be followed by longer remission than would otherwise have occurred.

The implications of this study with regard to treatment of patients are simple. Women who suffer from disseminated sclerosis should receive care during childbirth to make it as easy a time as possible and they should be relieved of as much strain and work as possible in the puerperium.

It will be appreciated that in a retrospective study such as this no account has been taken of severity of relapse or length of subsequent remission. Both these factors require investigation which, in our opinion, can only be achieved by careful documentation of future case histories so that errors due to faulty dating of relevant events can be eliminated.

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THE DISTURBANCE OF THE METABOLISM OF KETO-BODIES IN MULTIPLE SCLEROSIS

BY

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SEVERAL authors have dealt with the disturbances of carbohydrate metabolism of patients suffering from multiple sclerosis (M.S.) and particular emphasis has been given to anomalies of the metabolism of the keto-bodies. The results are, however, not always unanimous. According to Jones and co-workers (1950) the pyruvic acid values of the blood of fasting patients suffering from M.S. are higher than the normal ones. After oral administration of glucose to patients in various stages of the disease, the pyruvic acid content of the blood increases parallel with the activity of the process and the pyruvate lactate index also rises. Ervenich (1953) confirmed this finding and also observed a rise in the pyruvic acid content of the blood of fasting patients in the active stage of the disease and based the Berolase therapy which he introduced on this fact. Hennemann *et al.* (1954) also confirmed a disturbance of carbohydrate metabolism in the active stage of the disease. According to their observations after administration of glucose the lactic acid and pyruvic acid concentration of the blood rose to a small extent as compared to normal controls and the restoration of the blood sugar to the fasting level was also retarded. They found that the content of citric acid in the plasma and that of the α ketoglutaric acid of the whole blood was definitely higher.

Markees and co-workers (1954) as well as Gros *et al.* (1955) could not confirm the findings of Jones *et al.* (1950), relating to the higher fasting pyruvic acid for they only found it in one-third of the patients and in these cases it hardly exceeded the upper limit of the normal range. Furthermore, with respect to the pyruvic acid level of the blood they could not confirm the favourable effect of the Berolase therapy introduced by Ervenich. They believed that this disturbance of carbohydrate metabolism was not specific as this could also be demonstrated in patients with various liver diseases.

Gurjevics (1948) stated that in patients suffering from parenchymal liver diseases, hypertension, diffuse glomerulonephritis, pernicious

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anæmia and with an œdematous state of nephrosclerosis, the pyruvate level in the blood is raised.

Kleeberg and Gitelson (1954) observed that the pyruvic acid concentration of the blood of patients with cardiac decompensation was higher and was parallel to the degree of compensation, while Korting and Brehm (1956) found abnormal levels in patients with various diseases of the skin.

Hein-Sekula and Siedek (1953) as well as Coste *et al.* (1951) succeeded in raising the pyruvic acid content of the blood following ACTH and cortisone administration, and they attributed an important role to the hypophysis-adrenal system in the regulation of the pyruvic acid level of the blood. On the other hand, Markees (1954) did not believe that the rise in the blood pyruvate induced by a hexose load is a specific reaction of the activation of the hypophysis-adrenal system considering that following a combined administration of different drugs and vitamins, exerting an an influence on metabolism, he did not find any difference in the pyruvate level of the blood of normal, hypophysectomized or epinephrectomized animals. Considering that after an intravenous sugar load he succeeded by a combined administration of sympathico- and parasympathicolytic drugs in lowering the pyruvate level of the blood, he attributed the regulation of pyruvic acid to the vegetative nervous system rather than to humoral factors.

Bauer (1956) drew a parallel between the higher pyruvic acid values of the blood with the degree of spasticity and simply assumed that a muscle spasm was the cause of the higher pyruvic acid level of the blood demonstrated with the method applied by the above authors.

As it might be difficult clinically to determine the degree of activity of the disease in any one patient, it seemed preferable not to wait until an active phase set in, but to attempt to gain an insight into the various responses of each patient to artificial loads. Artificial fever was therefore induced and the disturbances of carbohydrate metabolism followed.

Method

After three to six days of rest fasting blood samples were taken following which 10 ml. sterile milk was administered intramuscularly. When the fever rose to 38° C. blood samples were again taken and during this period the patients were not allowed to move. Normal subjects, acting as controls, were submitted to the same procedures. Blood sugar was determined according to the method of Hagedorn and Jensen (1923*a*, *b*), pyruvic acid by the method of Friedemann and Haugen (1943), lactic acid according to Barker and Summerson (1941) and citric acid with the method of Natelson, Lugovoy and Pincus (1947).

Results

Table I shows the range obtained for the fasting pyruvic acid content of the blood in 152 patients with M.S. and these were not significantly different from the figures found in 114 control subjects.

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TABLE I.—PYRUVIC ACID CONTENT OF THE BLOOD OF FASTED MULTIPLE SCLEROSIS AND CONTROL PATIENTS

	Multiple sclerosis	*Control*
No. of cases	152	114
Range of pyruvic acid values of the blood of fasted patients ..	0·47–2·32 mg. per cent	0·35–2·00 mg. per cent
Mean values	0·853 mg. per cent	0·844 mg. per cent

No differences could be found between the blood sugar levels of the control subjects and the M.S. patients.

The blood pyruvic acid of 34 M.S. patients, at varying stages of the disease, was estimated before and after a rise of temperature to 38° C. and compared with results obtained in a similar manner from 25 control subjects suffering from various neurotic and spastic symptoms.

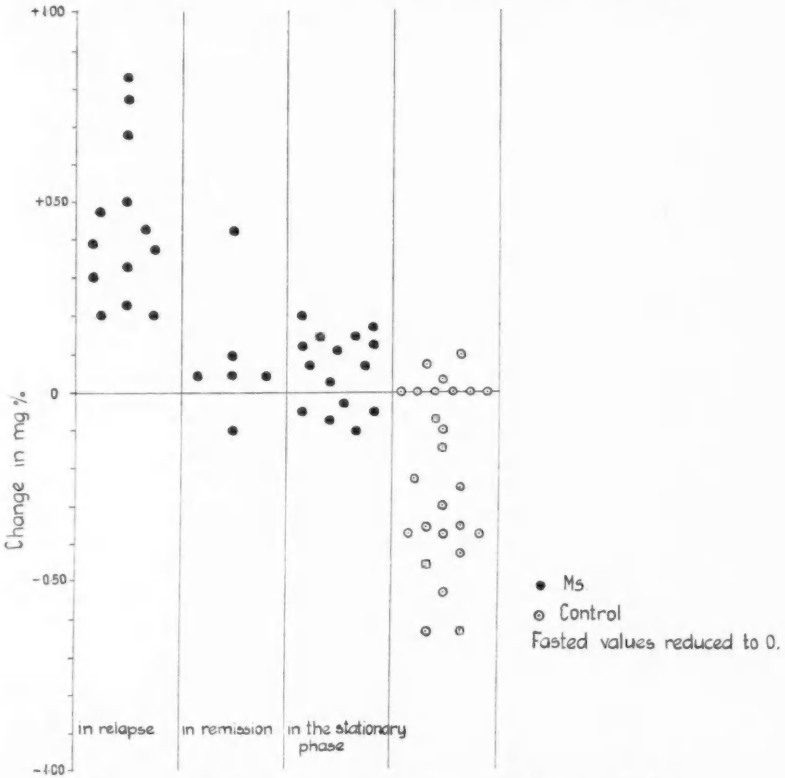

FIG. 1.—The pyruvic acid content in the blood of febrile patients.

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The results as seen in fig. 1 reveal that the M.S. patients show a mean rise of 0·21 mg./100 ml. after the increase in body temperature, whereas the control group show a fall of 0·22 mg. per 100 ml. Considering each group separately there is a mean rise of 0·43, 0·11 and 0·06 mg. per 100 ml. in the active phase, in a remission and in a stationary phase (unchanged for two years) respectively. The greatest alteration is seen in the period of active illness.

Simultaneous pyruvic and lactic acid determinations were made in 8 M.S. patients and in 9 control subjects. No significant changes were found.

In further investigations it was attempted to shed some light on the reason for the accumulation of pyruvic acid in the febrile M.S. patient. In the first place it was assumed that in the febrile state—particularly in its initial period—owing to the enhanced spasticity of the muscles—more pyruvate was produced. It is known that during muscle activity more pyruvate forms. The pyruvate which formed when the M.S. and the control patients had to carry out standard muscle work (10 deep squats and 10 grips with both hands simultaneously) was as quickly metabolized in the M.S. patients as in the control subjects.

In the following experimental series 0·02 gramme per kg. sodium pyruvate was administered intravenously to the M.S. and the control patients in their febrile and afebrile states. As can be seen in figs. 2 and 3, the M.S. patients eliminate the intravenously administered pyruvate in the febrile and afebrile periods just as rapidly as did the

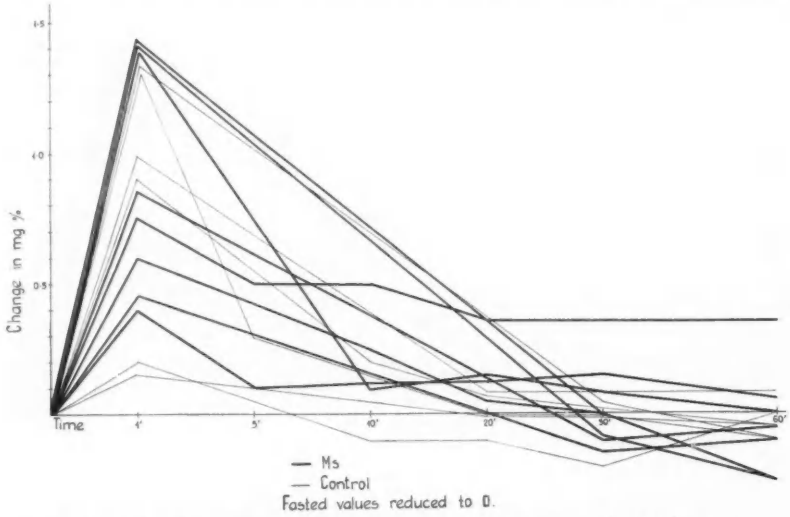

FIG. 2.—The disappearance of intravenous sodium pyruvate in afebrile state.

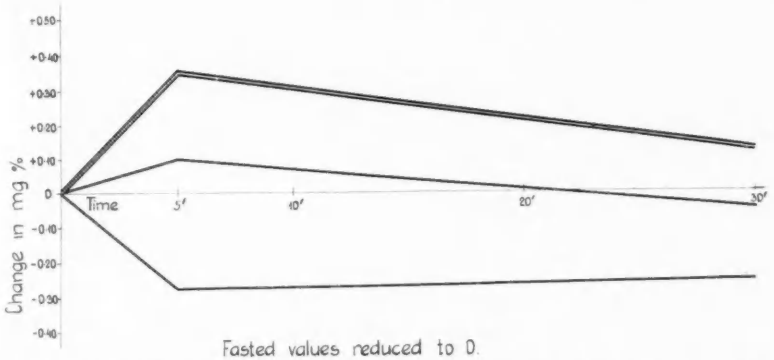

FIG. 3.—The disappearance of intravenous sodium pyruvate in febrile multiple sclerosis patients.

controls. In the case of febrile and afebrile M.S. patients the rate of the disappearance of the pyruvate is uniform.

According to the investigations of Domonkos and Huszák (1956) the carbohydrate metabolism of surviving brain tissue slices changed parallel with the hydrogen-ion concentration of the medium. Between the relatively small pH intervals at the shift towards the alkaline side the sugar utilization, aerobic lactic acid and pyruvic acid production of the surviving tissues increased, whereas the oxygen uptake and the formation of high energy phosphates remained unchanged. On the basis of these results after glucose administration *per os.* and intravenous alkalization with $NaHCO_3$ the changes of the blood sugar, pyruvic and lactic acid values were examined in M.S. patients. To 5 fasting M.S. patients and 5 fasting controls 50 grammes glucose *per os* were administered and subsequently the concentration of the sugar, pyruvic acid and lactic acid content of the blood were examined at intervals of one hour. These examinations were repeated the next day and combined with the intravenous injection of 40 ml. of 8 per cent $NaHCO_3$. The results are demonstrated in fig. 4. Both in the case of the M.S. patients and the controls the administration of $NaHCO_3$ alone promptly raised the pyruvic acid and lactic acid level of the blood, while the blood sugar level remained unchanged.

If the intravenous $NaHCO_3$ administration was combined with an oral glucose load the production of pyruvic and lactic acid was higher in the case of the M.S. patients than in that of the controls, in spite of this the pyruvate/lactate (P/L) index did not change as compared to the state before the load, or by comparison with the P/L index of the controls, rather showed a decrease.

The citric acid level in the blood of M.S. patients in the artificial febrile

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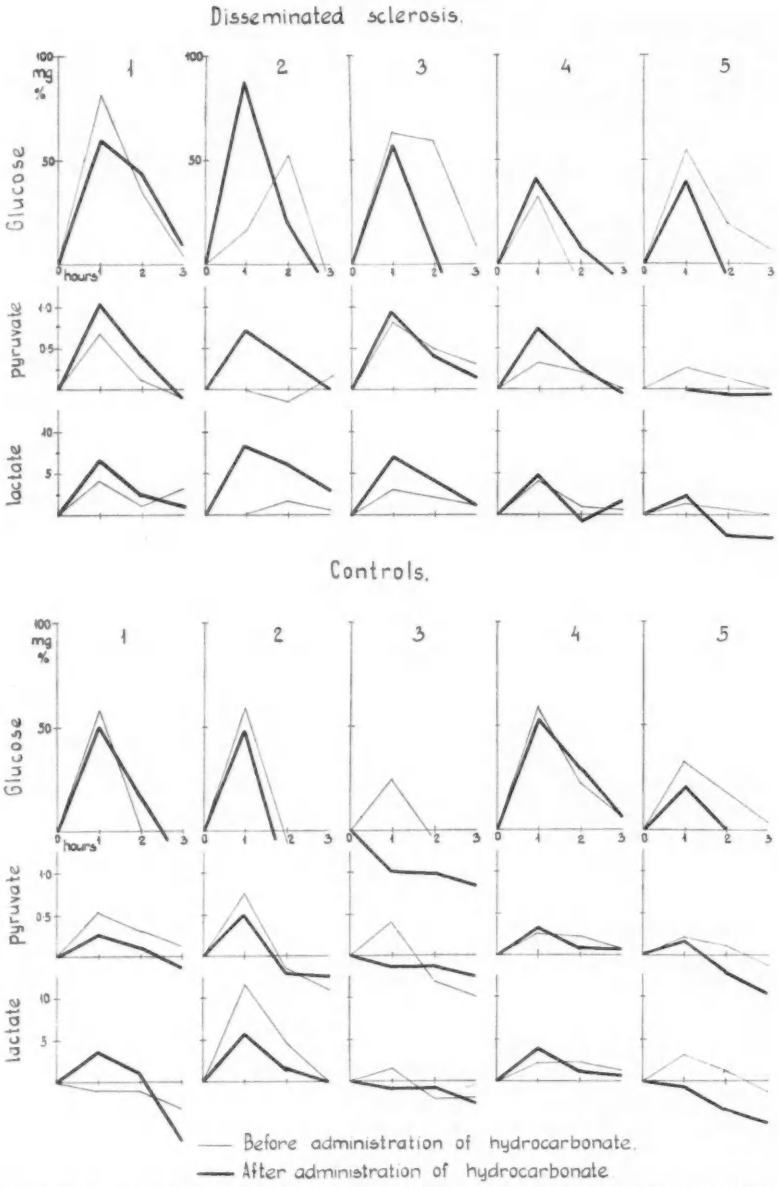

FIG. 4.—Glucose, pyruvic acid and lactic acid content of the blood following oral administration of glucose.

state showed an increase similar to that of pyruvic acid, but was more pronounced and this was independent of the activity of the disease. The average rise of the citric acid level in the blood of these patients was 0·27 mg. per 100 ml., whereas in the controls it was only 0·032 mg. per 100 ml.

Experiments with citrate loads were also carried out in M.S. and control patients in the febrile and afebrile state. Sodium citrate (0·01 grammes per kg.) administered intravenously disappeared from the circulation at a rate stimilar to that found in the controls.

As to the behaviour of the inorganic phosphate level, the conclusion can be drawn that independently of the phase of the disease in the patient there is an increased amount present at 38° C., whereas in the controls it is lower in the febrile state. The reason why the behaviour of the inorganic phosphate level is different in the controls will be analysed in a following paper.

Discussion

The causes of pathological phenomena should be analysed on the basis of the principle of the inseparable unity of the structural, functional and metabolic processes. According to the correlated systems of the biochemical processes of the body, it cannot be imagined that any single pathological tissue reaction represents an isolated organic phenomenon. Structural damages which may be found in an organ do not mean that the causes leading to the damage are only localized in that organ. In demyelinating diseases the disintegration of the myelin sheaths of the neurone is the most striking phenomenon. The white matter is, from a colloid chemical point of view, as well as owing to its low metabolic process, the most sensitive system of the body (Huszák, 1958). Hence, it is not surprising that the most varying pathological effects may lead to disintegration of the myelin sheath. In every cell the intactness and organized state of the structure during function and in the resting state is maintained by energy producing oxidation processes. An inhibition exerted by some pathological agent on a member of the fairly complex oxidation reduction enzyme system, or the lack of metabolizable products (as in insulin hypoglycæmia), or a disturbance in the oxygen supply may lead to a structural impairment of the cell. Therefore, in the white matter the most varied agents may lead to the disintegration of the myelin sheath.

According to these considerations the attempt should be made to analyse in detail the metabolic relations of the components of such an unknown pathological process as multiple sclerosis.

Glucose is almost the sole energy source of the oxidation processes in all nervous tissues. Such tissue builds up its higher fatty acids, e.g. acetylcholine and cholesterol from acetic acid which forms chiefly by

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the decarboxylation of pyruvate. This system may also be considered to be the cardan axis of the carbohydrate protein and fat metabolism. Thus it is understandable that in the case of multiple sclerosis some workers have directed their attention to the metabolism of these substances.

It is most important to bring the evaluation of laboratory results into correlation with the different phases of the illness. As the active, reparative and stationary periods of the disease cannot always be well differentiated clinically. The correct evaluation of laboratory data obtained is also difficult. The many discrepancies contained in the literature may partly be due to this fact. Taking these considerations into account it seems preferable to examine the responses of the pathomechanism to various well-defined loads. If loads are applied to pathologically impaired or less efficient enzyme systems the functional or metabolic disturbances ensue earlier in the region of the "weaker" enzyme system.

Owing to the above considerations, therefore, instead of concentrating our attention on the various chemical changes occurring in the blood in the different phases of the disease we have rather observed the various alterations resulting from varying loads. Patients suffering from the different phases of this disease were submitted to different loads and fever induced by milk proved to be a most suitable means. The advantage of milk as compared to other pyrogen substances is that after relatively mild shivering the temperature rises slowly. A temperature of 38° C. seemed to be the most appropriate as at this temperature the electrolyte metabolism and the changes in the eosinophil cell count as compared with results in control subjects showed a characteristic difference (Domonkos *et al.*, 1958; Könyves-Kolonics *et al.*, 1958).

The pyruvic acid values of the fasting patients reported in the present paper were in good agreement with normal values already reported in the literature. Thus the higher pyruvic acid values found by other authors mentioned above in fasting M.S. patients in the active phase has not been confirmed (fig. 1).

The results which we have found show a higher blood pyruvate in M.S. patients in the febrile state than in the controls and that the increase is greatest in the active phase of the disease. With the possibilities available it is not an easy task to establish either the reason for pyruvate accumulation in the blood, or where this takes place. The increased pyruvate, lactate formation may be due on the one hand, to the enhanced activity of the aerobic glycolysing tissues or on the other hand, to something interfering with the pyruvate-lactate oxidation pathway, or to its metabolism.

It is a well-known fact that in a febrile state the metabolic processes become enhanced and that in the healthy subject metabolism can take

the place of the intermediate products resulting from the increased sugar utilization. M.S. patients may not do this and in this way lactate-pyruvate may accumulate. The accumulation of the lactate-pyruvate may be partly due to the fact that the further utilization and oxidation of these substances is disturbed. This consideration induced us to administer pyruvate to M.S. patients and controls during febrile and afebrile periods (*see* figs. 2 and 3). Although the pyruvate blood level almost doubled the patients were able to eliminate this amount of pyruvate during the same period as the control subjects, even though this rise in the blood pyruvate level was higher than the rise occurring in the febrile state. The excess of pyruvate caused by enhanced muscle action is also as quickly eliminated by patients as by controls.

The rise of the blood pyruvate level induced by an experimental pyruvate load and muscle action lasts only a short time as compared to the pyruvate rise following fever, and it may be that the patient can deal with the former situation but would not be able to metabolize adequately a continuously higher pyruvate production.

Enhanced glycolysis of the tissues may also represent one of the causes of the pyruvate-lactate accumulation found in febrile M.S. patients. It would then be expected that the inorganic phosphate content would decrease. This actually occurred in the febrile controls, but a rise in the inorganic phosphate content took place in the greater number of the patients.

If sodium hydrocarbonate is injected intravenously it inhibits the rise in the P/L index following a sugar load in M.S. patients. On giving sodium hydrocarbonate intravenously without sugar a prompt increase of the pyruvic and lactic acid content of the blood follows. This is in good agreement with the results of the *in vitro* experiments of Domonkos and Huszák according to which sugar utilization, pyruvic and lactic acid production of the surviving brain slices increased when there was an alkaline shift of pH. But whereas in their experiments the P/L index rose if an alkaline shift took place, in our *in vivo* investigations an increase in the P/L index could not be observed either in patients or in controls. This may be explained by the fact that possibly the body may metabolize the pyruvic acid which forms by alkalinization *in vivo* more rapidly than the excess of lactic acid.

The accumulation of pyruvate-lactate in the blood of febrile M.S. patients accompanied by an increase of inorganic phosphorus points to a disturbance of carbohydrate metabolism. The increase of citric acid under the same conditions also indicates a similar disturbance.

We believe that this abnormality in inorganic phosphate level of febrile M.S. patients is an important phenomenon which must be further investigated and may lead to the better understanding of the carbohydrate metabolism of M.S. patients.

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SUMMARY

The fasting blood pyruvic acid in M.S. patients in the resting state is not higher than that of control subjects. Following an artificially induced milk fever at a temperature of 38° C., M.S. patients show an accumulation of pyruvic acid in the blood which is in proportion to the activity of the disease. The pyruvate-lactate index, however, does not show a significant increase. The citric acid content of the blood of febrile patients increases similarly at a temperature of 38° C. This increase, however, does not run parallel with the activity of the process.

If sodium hydrocarbonate is given intravenously together with oral glucose, there is a significant increase of pyruvic and lactic acid. Intravenously injected pyruvate and citrate is as quickly eliminated by patients as by controls. The inorganic phosphate content of the blood increases in patients at 38° C., whereas in control subjects it decreases.

The problem of the accumulation of endogenous pyruvic acid of multiple sclerosis patients with fever is discussed.

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DISORDERS OF "SIMULTANEOUS PERCEPTION" IN A CASE OF BILATERAL OCCIPITO-PARIETAL BRAIN INJURY

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I. Introduction

In reports of the optico-gnostic disorders arising from cerebral lesions, a restriction of the field of visual perception to single objects or their parts has been repeatedly described. It was mentioned in some of the earliest descriptions of visual agnosia (Wilbrandt, 1887; Lissauer, 1890) and subsequently analysed with particular thoroughness by Bálint (1909). In Bálint's case, the patient was said to have been able to see only one object at a time, irrespective of its size. Holmes later described very similar disorders in cases of bilateral posterior parietal gunshot wound (Holmes, 1919; Holmes and Horrax, 1919). Although placing the main emphasis upon loss of visual orientation, Holmes referred to a constriction of visual attention as an important element in the syndrome. In more recent years, Bálint's syndrome has been reinvestigated by Hécaen and Ajuriaguerra (1954), who likewise stress the defect of attention and the bilaterality of the responsible lesion.

Defects of visual synthesis of a somewhat less pronounced character have also been described in the literature (Gelb and Goldstein, 1920; Wolpert, 1924; Head, 1926; Paterson and Zangwill, 1944). In these cases, the lesion is commonly unilateral, orientation in space is usually preserved, and scanning movements of the eyes less obviously disturbed. But there may be gross incapacity to combine the elements of the perceptual display into a coherent and integrated whole. To this type of deficit the term "simultanagnosia" is commonly applied (Wolpert, 1924).

It is clear that the limited and fragmentary character of perception so often associated with occipito-parietal lesions cannot be wholly accounted for in terms of visual field defects. Restriction of visual perception to individual objects or their parts has been described in the absence of significant field defects; conversely, perception may be more or less adequate in spite of extensive scotomata. This is not, however, to say that the perceptual deficit does not call for physiological explanation;

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indeed the need for such explanation has been repeatedly stressed in the recent literature and at least two theories of its origin (Bay, 1950; Denny-Brown, Meyer and Horenstein, 1952) have been put forward.

It is the author's belief that a proper explanation of the occipito-parietal syndromes will come about only through thorough investigation of the neurodynamical basis of agnosic states. Such an investigation should proceed from the principles of physiological analysis adumbrated in the modern Pavlovian theory of higher nervous activity.

In 1935, I. P. Pavlov devoted one of his "Wednesday colloquia" to the discussion of a case of brain injury briefly reported by Pierre Janet (1935, pp. 160–3). This was the case of a French officer who sustained a bilateral occipital gunshot wound and who subsequently presented a peculiar disturbance of vision. According to Janet, "visual comprehension became concentrated" and the patient lost the ability of orientation in space. He could not see a number of objects simultaneously and, in his own words, "felt lost in the surrounding world."

The physiological analysis of this phenomenon given by Pavlov is of exceptional interest. "The (occipital) region," he wrote, . . . is inhibited to such a considerable degree that it cannot endure two simultaneous stimulations . . . . The visual region of the brain has such a low tonus of excitation that it is able, influenced by the given stimulus, to concentrate its activity at one point only, while all other points remain as if they were non-existent. Hence the patient sees a distinct person, a distinct object, but he is unable simultaneously to perceive anything else, since the notion of space escapes him. Everything is confined to the point which is stimulated at the given moment. There are no traces whatever, and that is why the patient feels 'lost in the world' (Pavlov, 1955, p. 609).

Pavlov's attempt to consider physiologically the origin of central visual disorder opens up bright prospects. If we assume that, owing to the functional weakness of the visual cortex, each focus of excitation inhibits the remainder of the cortex by way of negative induction, a functional limitation of perception must inevitably result. This viewpoint makes it possible for us to comprehend "restriction of visual attention" in physiological terms and to approach the phenomena of "simultaneous agnosia" in a new way. For the deficit will then appear as a consequence of excessive cortical inhibition, leading to failure to synthesize excitation arising in the visual sphere under conditions of complex stimulation. One might also suggest that a patient whose perception is restricted to a single detail will be obliged to combine details in a *secondary way*, relying on his intact speech to attempt an interpretation of the total situation.

This hypothesis can be verified only through thorough investigation of appropriate clinical cases. It must be established first, that agnosic disorders of the kind described by Janet really are referable to want of

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simultaneous perception: and secondly, that they really are determined by neurodynamic disturbance of the cortex and are subject to modification by factors which influence cortical tonus. We propose in the present paper to attempt to answer these questions by reference to a detailed analysis of a case of brain injury closely comparable to that of Janet to which reference was made by Pavlov.[1]

II. Case Report

V. . ., aged 21, an officer of the Polish Army, was wounded in the left occipito-parietal region in April, 1945. The bullet penetrated through the posterior and mesial parts of this area, crossing the mid-line and becoming embedded in the oral parts of the right occipital lobe. It may be assumed that the bullet passed either through the splenium of the corpus collosum or dorsally through the large longitudinal ligament and the white matter of both occipital lobes (fig. 1).

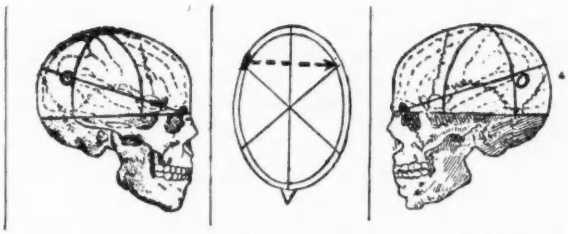

Fig. 1.—Patient V. . . Approximate locus and track of missile wound.

The patient at first presented a left-sided hemiplegia and motor aphasia. Vision was totally lost. Six months later, speech was fully recovered and some improvement of the hemiplegia was in evidence. Vision began to improve. The patient at this stage reported attacks of giddiness and nausea as well as photophobia and epiphora, i.e., symptoms which testify to an irritation of the corresponding parts of the brain.

Six months later, the patient underwent a trepanation of the right occipital lobe with a view to removal of the m.f.b. (this operation was however unsuccessful, the m.f.b. being removed at a later stage at the Institute of Neurosurgery in Moscow). After the operation the patient's vision again deteriorated, without further improvement. The attacks of vestibular giddiness were now accompanied by epileptic fits, which began with acute headaches and twitching of the right eyelid, and were associated with loss of consciousness. These attacks necessitated his readmission to the Burdenko Institute of Neurosurgery in Moscow, where he had already undergone treatment in December 1947 and in August–October 1950.

At this time the patient's behaviour was absolutely normal. He spoke Polish and Russian without difficulty: vocabulary and grammar were fully intact. He could

[1]Phenomena essentially similar to those described here may also arise on a paroxysmal basis. I have had occasion to observe a boy of 14, who suffered from epileptic attacks accompanied by micropsia following an occipito-parietal injury at the age of 9. Before each fit the boy's field of visual perception was limited in such a way that he could see only *one* object at a time, e.g. a letter, a car, or a man, irrespective of its size. The analysis of paroxysmal visual defects of this type might be expected to throw valuable light on the functions of the visual cortex.

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repeat 6 or 7 words or digits forwards. Understanding of speech was intact and the patient readily performed various abstract operations, experiencing difficulty only when it was necessary to appreciate spatial relationships directly based on visual analysis. He could easily carry out complex verbal instructions (e.g. Marie's test). Calculations were easily performed and the patient could grasp the logical system of rather complex arithmetical problems. Emotionally, he was absolutely normal, and tried hard to overcome his disabilities.

The patient's main complaint was of certain defects in his vision which he could not, however, clearly specify. He stated that he discerned objects around him with difficulty, that they flashed before his eyes and sometimes disappeared from his field of vision. This impression was particularly pronounced in reading: the words and lines flashed before his eyes and now one, now another, extraneous word suddenly intruded itself into the text. The same occurred in writing: the patient was unable to bring the letters into correlation with his lines or to follow visually what he was writing down: letters disappeared from the field of vision, overlapped with one another and did not coincide with the limits of the lines.

The patient also complained of occasional attacks of giddiness and of infrequent fits, with visual and kinesthetic auræ, and accompanied by loss of consciousness.

On *neurological examination* (Dr. Podgornaya), the main findings were residual left-sided hemiparesis, most pronounced in the proximal parts of the limbs, increase of tendon reflexes, and some trophic changes in the left limbs. Sensory findings comprised diminution of sensitivity to temperature and pin prick in left limbs and left-sided astereognosis.

Neuro-ophthalmological examination (Dr. Pantieleva) revealed a slight pallor of the optic discs and some degree of concentric constriction of the visual fields (fig. 2). Visual acuity was normal. No abnormality of colour vision.

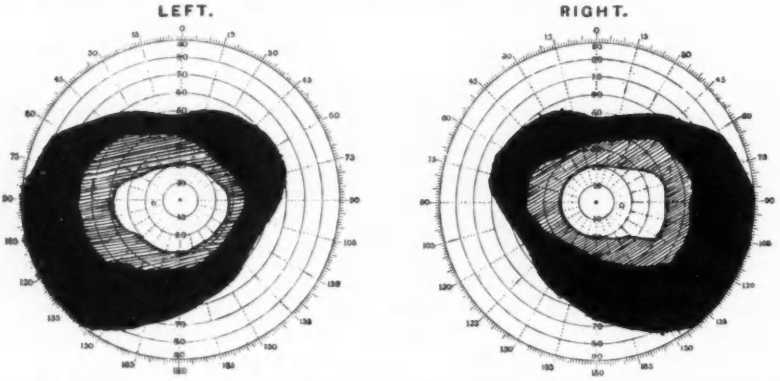

FIG. 2.—Visual fields of patient V. . . Stippled area: Movement perception only.

At *otological examination* (Professor Ageyeva-Maikova), auditory sensitivity was found to be intact but there was marked derangement of binaural hearing. The patient exhibited a slight spontaneous nystagmus.

Electroencephalographic studies (Dr. Novikova) gave evidence of a marked deceleration of the alpha rhythm in the occipital region, accompanied by slow delta waves. The latter were more pronounced on the right side and sometimes irradiated

over the whole cortex. The normal depression of the alpha rhythm to visual stimulation was reduced, particularly on the right side.

X-ray studies (Professor Kopylov) indicated phenomena of regional hydrocephalus, especially in the posterior portions of both ventricles. The posterior horn of the left lateral ventricle showed marked dilatation and the posterior and lower horns of the right lateral ventricle were obliterated, due to productive cicatricial changes. These findings testified to a residual inflammatory process in the occipital region.

This patient presents clear indications of a bilateral occipito-parietal lesion. There are obvious disturbances in optico-vestibular and visual functions, which the patient himself could not clearly specify. At the same time, speech remained intact and the personality was well preserved.

III. Defects of Visual Perception

The patient was able to perceive objects in an essentially normal manner. He could recognize geometrical figures (e.g. triangle, square), even when they were drawn in dotted lines. Substantial defects made their appearance only when *the visual field contained a number of separate elements*. Under these conditions the process of perception was greatly retarded. The patient moved his eyes from one object to another in a confused and inadequate manner. Thus it might take him 7 or 8 seconds to perceive a group of three small objects. Oculomotor scanning often appeared defective, leading to failure to fixate one or more of the objects present (those to his left being more frequently ignored).

These findings suggested that there was an appreciable derangement of *simultaneous visual synthesis*, which should also appear under conditions in which eye movements were excluded. A series of tachistoscopic experiments were therefore undertaken.

Tachistoscopic studies: Groups of 2, 3 and 4 single figures were repeatedly presented on cards of 2 × 3 cm. or 3 × 4 cm., each card being exposed such that the material fell fully within the intact portion of the visual field. Exposure times varied between 0·2 and 0·6 sec., and were occasionally raised to 0·8 sec. Illustrations of the displays used are given in fig. 3 (a–d) and 4 (a and b).

Experiment 1 (fig. 3a): Twenty-five presentations of this display were given. On only three of these (Trials 20, 23 and 24) were both forms correctly recognized. The circle alone was reported on ten occasions and the cross alone on three. In seven cases, one figure was correctly recognized and the subject also reported a second figure, which he was either unable to name or which he misidentified. In five cases, neither figure was perceived. It was noteworthy that, even when the patient was told that a cross was present in addition to a circle, he still failed to perceive the former figure.

Experiment 2 (fig. 3b): On eighteen presentations of this display, the circle alone was reported once and the square alone once. "A square and a dot" were reported on four occasions and "a circle and

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a dot" on one. In the remaining cases either nothing was seen, or one or more "dots."

Experiment 3 (fig. 3c): Nine presentations were given. The star alone was reported on four occasions, and a star "with something else" on three. On one exposure, the patient reported "a star and a triangle or a circle. I could not make it out."

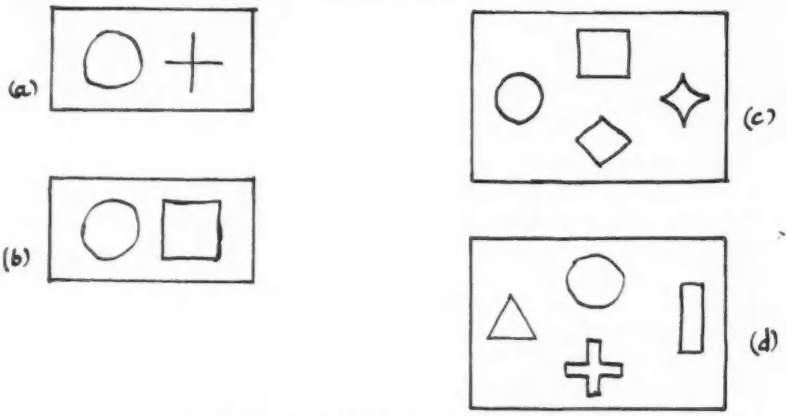

FIG. 3.—Experiments 1–4: Simultaneous exposure of simple forms.

Experiment 4 (fig. 3d): Ten presentations were given. A cross with or without "something else" was reported on six occasions. "A double rod" was reported three times.

Experiment 5 (fig. 4a): Seven presentations of this display were given. One triangle was perceived on the first and third exposures. On and after the fourth presentation, however, both triangles were noted.

FIG. 4.—Experiments 5–6: Simultaneous exposure of identical or related forms.

Experiment 6 (fig. 4b): Ten presentations were given. One circle was perceived on the first four trials. Thereafter, the patient consistently reported "two circles, resembling spectacles."

These results suggest first, that when two or more separate forms are exposed for brief intervals, only one is seen at a time; and secondly, that if the two forms are identical, or combined into a single structure, their perception is markedly facilitated.

It may therefore be postulated that the excitation evoked in the visual cortex was confined to a single focus. In some cases, this focus represented a single objective "element," in others, a configuration composed of several "elements," e.g. "spectacles." But if the several "elements" did not form a configuration, and thereby required for perception the synthesis of two isolated centres of excitation, the patient was in general unable to perceive them simultaneously. This was clearly brought out in the following experiments:

Experiment 7 (fig. 5a and b): A star-shaped figure consisting of two overlapping triangles (5a) was exposed for a short interval. The patient immediately perceived it as a star. If, however, one triangle was coloured red and the other blue (fig. 5b), *one or other triangle*

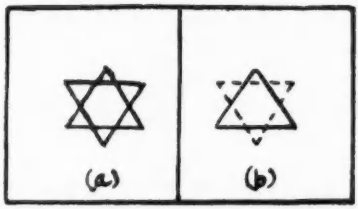

FIG. 5.—Experiment 7: Effects of colour on form perception.—: red – – –: blue.

alone was perceived and the star was never reported. In the same way, a very simple outline drawing of a human face was recognized if all components were drawn in the same colour, but never recognized if two different colours were employed. In general, the more complex the coloured material, the greater the recognition difficulty.

These results indicate that, owing to constriction of the perceptual field (in particular disregard of the left half), the patient is unable to perceive a number of visual items presented simultaneously. In such a patient, the visual cortex can "concentrate its activity at one point only, while other points remain as if they were non-existent." It is only where, in virtue of previous experience, several stimuli can be combined into a single configuration that the simultaneous perception of several elements becomes possible.

IV. OCULOMOTOR "ATAXIA"

The perceptual restriction to which we have called attention was associated with a second, and probably related, syndrome which has often been described in the literature. This consists of a derangement in oculomotor scanning and "ataxia of the gaze" (Bálint, 1909; Hécaen and Ajuriaguerra, 1954).

Although the patient was able to control movements of his right upper limb very adequately with eye closed, his movements lost all precision

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when executed under the control of vision. It took him much time to locate and grasp an object placed upon the table; his movements were clumsy and he often missed the object altogether. It is characteristic that his "gaze" manifested the same helplessness as his arm.

This lack of proper oculomotor scanning was also apparent in reading and writing. In reading, extraneous words would intrude themselves into his field of vision; in writing, the patient proved unable properly to dispose the elements of the letters in space and to co-ordinate his writing with the lines (fig. 6a). If, however, he attempted to write with eyes closed (fig. 6b), performance was consistently improved.

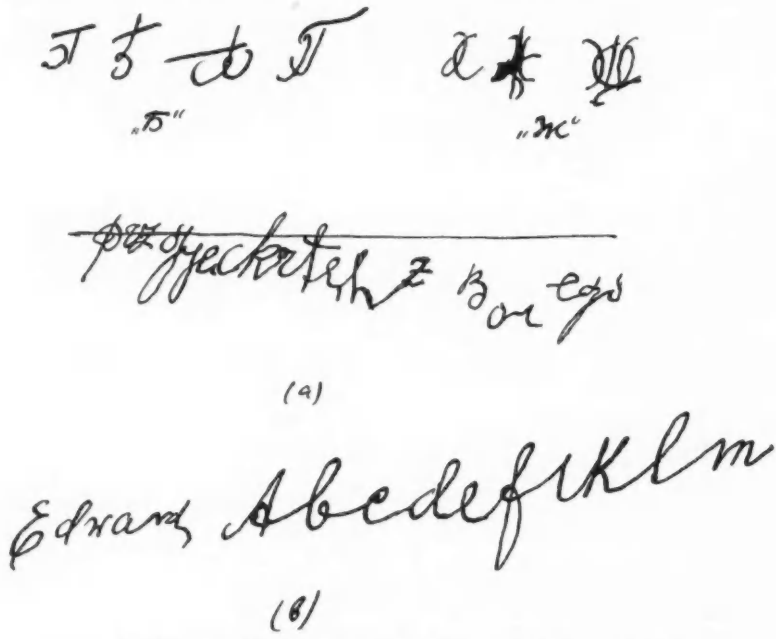

FIG. 6.—Samples of writing: (A) Eyes open. (B) Eyes closed.

These findings suggest that the derangements in motor performance, both manual and oculomotor, would appear to originate on a predominantly visual basis. But it remains to be ascertained whether, and if so to what extent, they are connected with the postulated changes in the activity of the visual cortex to which attention has been drawn.

A series of experiments was carried out to determine the extent to which the defect in simultaneous visual conjunction is reflected in motor co-ordinations.

Experiment 8: The patient was first asked to touch with the tip of a pencil a *single* dot presented on a piece of paper. This he could do quite adequately. If, however, the examiner pointed to a given spot on the paper (without making any mark) and then asked the patient to point to the same spot, the task proved exceedingly difficult and quite extensive errors (2 or 3 cm. deviation) were recorded.

Still greater difficulties arose if the patient was required to co-ordinate his movements in accordance with the relationship between a number of visual elements; e.g. to place his pencil point on the centre of a circle or cross. Thus he would complain that one line of the cross would disappear while he was fixating the other. He also tended, when fixating the point of the pencil, to "lose" the design. For this reason, the patient tended to adopt special procedures to avoid having to perceive all the relevant elements simultaneously. Thus he might move his pencil along one of the lines of a cross, or view the cross from above and make a sudden jab with his pencil towards its centre.

Very similar difficulties likewise arose if the patient were required to outline a figure (fig. 7a and b) or to copy a design.

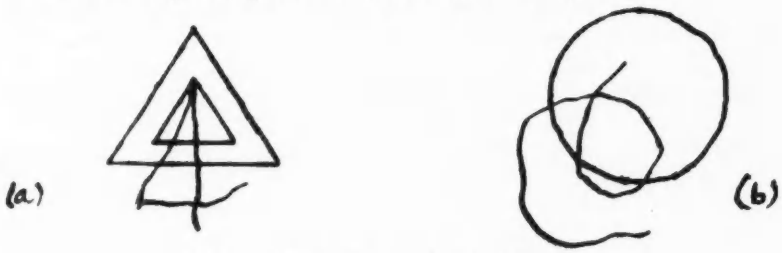

FIG. 7.—Attempts to outline simple figures.

It is plain that if there is but a *single* focus of excitation in the visual field, the act of visual fixation of the corresponding object remains relatively undisturbed. If, however, we deal only with the *trace* of such an excitation (as when the patient is required to indicate a spot touched a second or two previously by the examiner), the weakened visual cortex manifests a considerable defect in the concentration of nervous activity. The trace is extremely unstable and considerable error results. Finally, the patient's incapacity to perceive two elements simultaneously, and to co-ordinate fixation and manipulation in terms of a synthetic visual perception, evokes the phenomenon of "optic ataxia." This, to a considerable degree, represents the motor equivalent of the visual disorder.

V. VISUAL SYNTHESIS AND SPATIAL ORIENTATION

There is an apparent paradox in the fact that the patient can perceive a unified structure while being at the same time unable to appreciate a

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complex of unrelated elements. This paradox is, however, resolved when we bear in mind that the patient's appreciation of a perceptual structure may be lost if he is required to focus attention upon its component elements.

Experiment 9: If the patient is presented with a pattern of six dots arranged to form a rectangle, he can easily perceive and name it. But if the patient be then instructed to *count* the component dots, he experiences very considerable difficulty. The new task destroys immediate awareness of the configuration; it is now the separate elements which become the object of analysis. Under these conditions, the patient becomes unable to see clearly any dot other than that which he is immediately fixating. This simple experiment helps us to comprehend the peculiarities of the act of reading in our patient, as well as of his perception of complete and complex situations.

A picture presenting a definite situation is perceived by the patient as a whole, though he does not always obtain the correct idea of its nature. When he attempts to analyse it, however, difficulties arise of the kind described in the above experiment. Concentration on any given detail results in the loss of its relationship to the remainder and the general perception of the picture becomes disintegrated.

Experiment 10: A picture of two men talking on a verandah was shown to the patient. He immediately said: "Here are some people." When asked to specify the number of people, he pointed first to the head of one of the men, saying "one," then to the arm of the other, saying "two." He then pointed to the head of the same man, saying "Here's a third." Repetition leads to no improvement in comprehension; indeed to further disintegration of the original global impression.

The same basic want of visual synthesis was also apparent in the patient's weakness in spatial orientation. Although orientation for left and right (with regard to his own body or to external objects) was preserved, orientation in space was markedly deranged. According to his own statement, he had been at first unable to orient himself in his native town. "I was really ashamed," he said, "Although the town was so familiar to me I was compelled constantly to ask the way. Once I addressed such a request to a passer-by in the street; on the way back I happened to address the same person with the same request. Naturally he was surprised and wondered whether I was drunk. I apologised and decided to find my way without assistance."

Experiment 11: This defect of orientation was investigated by A. Y. Kolodnaya. It was found that the patient was quite unable to draw routes or ground-plans. When trying to draw a scheme of his ward, he proved unable to represent the disposition of objects and was compelled to examine each individual object afresh to ascertain

its place in the ward. As a result, the simple task of drawing a scheme of the ward was fulfilled in the form of numerous separate observations and was in consequence extremely time-consuming. (On one occasion he took 40 minutes over the task, which involved turning the head or even the entire body 110 times.) It was also characteristic that the patient, when drawing the scheme with his back to the ward, represented it mirror-wise without appropriate transposition.

The principal defect underlying the loss of orientation thus appears to be a limitation of perception to one element and an inability to reflect the inter-connection of attributes in visual perception or imagination. This resulted in a syndrome close to that formerly described as "simultaneous agnosia."

VI. Effects of Caffeine on Visual Performance

Let us now attempt to approach this syndrome from the standpoint of Pavlovian neurodynamics.

If—as Pavlov assumed—a decline in tonus of the nervous processes in the affected visual cortex underlies this syndrome, it might be surmised that certain pharmacological agents, by affecting the general tonic state of the cortex, would produce alterations in the symptoms. The fact that only a relatively small part of the occipito-parietal area was wholly destroyed by the injury gave sufficient grounds to anticipate a positive result.

A series of experiments was carried out with injections of 10 per cent solution of caffeine (from 0·05 to 0·1 gramme). Control tests were carried out before and after the injections.

The experiments yielded distinctive results. The patient stated that all of a sudden everything appeared to him "in a brighter light" and he was able to accomplish in a new and direct way many tasks which normally gave him very considerable difficulty. These changes manifested themselves 15 to 20 minutes after the injection, and reached their maximum level in 30 to 35 minutes. Thereafter, they gradually declined, performance returning to the previous level after about one hour to one hour and a half.

(1) *Tachistoscopic perception of figures.*—Experiments of the kind described in Section II of this paper gave markedly different results 20 to 25 minutes after the injection of caffeine. In cases in which two simple figures were simultaneously exposed, perception of two figures was recorded in almost 50 per cent of exposures. A comparison of the findings with those obtained before and after the administration of caffeine is given in Table I. (In this Table, "incomplete" perception of the two figures refers to cases in which one figure alone was clearly perceived but the subject was aware that a second figure of some kind was also present.)

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TABLE I.—SIMULTANEOUS PERCEPTION OF FIGURES BEFORE AND AFTER INJECTION OF CAFFEINE

Time of test	*No. of combined exposures*	*Perception of one figure only*	*Perception of the figures*	
			Complete	*Incomplete*
(1) Prior to administration of caffeine	30	25	0	5
(2) 25 min. after injection of caffeine	30	14	12	4
(3) 1 hour after injection of caffeine	30	20	2	6

(2) *Visual-motor co-ordination.*—Performance on simple tests of visual-motor co-ordination was much improved by injection of caffeine. It was found that the patient, 15 to 20 minutes after an injection, could place a dot accurately in the centre of a circle or bring his pencil-point accurately to the centre of a cross. Further, he was able to perform these tasks in a direct way, without resorting to his usual "round about" methods. The average time taken to execute these two tasks was markedly reduced.

(3) *Visual analysis of patterns.*—Similar results were obtained with tests of counting dots arranged to form simple and regular patterns. As a rule, the patient was quite unable to count five dots arranged in a simple pattern. But 20 minutes after the administration of caffeine he performed the task easily and quickly, the effect persisting for about an hour.

(4) *Plan-drawings.*—A striking improvement in the ability to draw plans or routes was likewise observed. The task was performed very much more quickly and the level of representation much improved. Head-turning was much reduced, e.g. from 110 to 8 turns. As in the earlier experiments, the best results were obtained 25 to 30 mins. after the administration of caffeine and the effects persisted for 1–2 hours.

These findings suggest that the occipito-parietal injury had been instrumental in reducing the tonus of excitation in the visual area of the cortex. Increasing the level of tonus by pharmacological means led to marked, if transient, improvement in visual and oculomotor capacity.

VII. SUMMARY AND CONCLUSIONS

A case is described in which marked derangements of visual perception and orientation occurred as *sequelæ* of a bilateral occipito-parietal brain-injury. It is argued that the key feature of the syndrome is the restriction of visual perception to a single object or configuration. This deficit can best be explained in terms of Pavlov's theory of cortical activity. According to this theory, there is a general functional weakness (or reduction in cortical tonus) of the affected portions of the brain. In

consequence, each focus of excitation within this area inhibits the remainder of the visual cortex by way of negative induction. If, therefore, a large number of stimuli are simultaneously presented, only very few are likely to elicit a perceptual response. The patient is in consequence likely to perceive only a restricted element or aspect of the total stimulus pattern.

It is probable that an explanation of this kind will cover many of the phenomena of visual agnosia described in the literature. In particular, "limitation of visual attention" (Holmes), "incapacity to combine details into a coherent whole" (Head) and "piecemeal perception" (Paterson and Zangwill) would appear as no more than psychological consequences of this basic neuro-physiological deficit.

At the same time, it appears unlikely that such an explanation, in its present form at least, will cover all aspects of agnosia, in particular those which appear to betray an ideational or conceptual origin, e.g. true topographical agnosia. The more adequate understanding of these syndromes in terms of changes at the neurophysiological level remains a task for future research.

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SPECIFIC DEVELOPMENTAL DISORDERS OF SPEECH IN CHILDHOOD

BY

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In recent years there has been increased interest in the speech disorders of childhood, and as a result differential diagnosis has improved in accuracy (Morley, 1957).

In a recent series of 187 fully investigated patients referred to the Speech Clinic of the Royal Hospital for Sick Children, Edinburgh, 80 were diagnosed as suffering from "Specific Developmental Disorders of Speech." This category consists of speech defects which are characterized by the retarded development of the ability to articulate speech sounds accurately, and cannot be attributed to the presence of mental or emotional retardation or physical disease. A high proportion of patients have associated retardation of language development (developmental aphasia or dysphasia), difficulties in learning to write and read (specific dysgraphia and dyslexia). Many show little lateralization of handedness. There is often a family history of retarded speech development, ambidexterity or left handedness, and of educational difficulties (Ingram, 1959). It is the purpose of the present paper to review the clinical, psychological and speech characteristics of the 80 patients recently examined.

The Clinical Material and Method of Investigation

The Speech Clinic in the Royal Hospital for Sick Children caters for patients referred by general practitioners, doctors in local welfare clinics, school medical officers, and consultants in the various branches of pædiatric medicine and surgery. Since the speech therapy services in Corporation Schools in Edinburgh are highly organized, the majority of children in the city with speech defects are referred to them rather than to the Hospital. Thus the majority of cases seen in the present series were under the age of 5 years.

Patients referred are seen routinely by a screening panel consisting of a pædiatrician, speech therapist and psychologist. A detailed history is

taken from the parents or guardian. Particular attention is paid to any family history of speech disorders, the handedness of parents and siblings, the birth and developmental, social and medical history of the patients. Specific questions are asked about the nature of the child's speech defect; evidence of acute hearing is sought; reports of educational progress or behaviour in nurseries are obtained when possible.

Children are subjected to a routine pædiatric and detailed neurological examination. Speech is studied at the time of interview by the speech therapist and pædiatrician, and tape recordings are taken. Clinical tests of hearing are made at the time of the first examination. Pure tone audiometry is performed routinely as soon as the child can co-operate in this examination. A psychologist attached to the clinic assesses the child's intelligence in all cases and investigates educational difficulties when these occur. Handedness was tested by noting the hand which the child used in each of four tests used three times. Each patient was asked to turn a door handle, break a stick, throw and catch a ball. Eyedness was tested by observing the eye the child used in looking through a telescope placed in each hand and both hands, and by asking him to look through a hole in a piece of paper held by the examiner three times (a total of 6 tests). Footedness was tested by asking him to kick a ball three times, and by observing on three occasions the leading foot used when beginning to walk or climb, after being pushed from behind when necessary. Patients using one hand for less than nine of the total of twelve tests were classified as being ambidextrous. Patients using one foot or eye in five or more of the six tests were classified as right or left eyed or footed. Those using each foot or eye three or four times were classified as showing little lateralization of eyedness or footedness.

10 patients were seen by a child psychiatrist, 11 by an otolaryngologist, 2 by an orthodontist, and 18 parents were interviewed by a psychiatric social worker. 4 patients were admitted to hospital for further study on account of their speech defects, behaviour or because of associated abnormalities detected during the screening examinations.

The patients were asked to return to the screening clinic at three- or six-monthly intervals so that the development of their speech could be followed and the need for therapy reassessed periodically.

Findings in the Patients with Specific Developmental Speech Disorders

Social Conditions

Using the Registrar-General's categories, the Social Class of patients by the occupation of father, adoptive father or single mother was determined and is shown in Table I. It will be observed that there is a marked excess of patients in Social Classes I and II compared to all live births in Scotland (1951). This is probably a reflection of the greater

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TABLE I.—PATIENTS WITH DEVELOPMENTAL SPEECH DISORDERS BY AGE AT REFERRAL AND SOCIAL CLASS OF FATHERS COMPARED TO ALL LIVE BIRTHS IN SCOTLAND (1951)

	Social class of fathers					
Age	*I*	*II*	*III*	*IV*	*V*	*Total*
Under 3 years ..	1	1	3	0	0	5
3 years but under 4	8	5	8	4	2	27
4 years but under 5	8	4	14	3	4	33
5 years but under 7	6	3	2	1	0	12
7+	1	0	2	0	0	3
All ages	24	13	29	8	6	80
Approx. %	30	16·25	36·25	10	7·5	100
Approx. % all live births in Scotland	3·7	8·8	58·3	14·5	14·7	100

attention paid to defects of speech in the upper social classes than in the lower, rather than an indication of any actual difference in their prevalence. In particular, a number of private schools in Edinburgh take a very serious view of speech defects in childhood, though they rarely have speech therapy facilities of their own. Many children of professional parents were referred to have their speech "put right" a few weeks or months before their entrance examinations to these schools.

7 children were illegitimate. 3 of these had been adopted, 1 was living in an institution, and 3 were with their mothers, 1 of whom had subsequently married. In 4 other cases the parents were separated at the time of screening interview. In 4 cases the fathers had been unemployed for long periods and there was relative poverty in the families. 4 of the mothers were in full-time employment and 13 were in part-time employment. In at least 8 cases it seemed probable that the patients were not seeing enough of their mothers.

Family History

The details of speech and hearing defects, educational difficulties and the handedness of parents and siblings were obtained from the parents. It was impossible to confirm all the information they gave from other sources or by direct examination. This was particularly unfortunate because it prevented any reliable assessment of the prevalence of speech defects amongst parents and siblings. The figures obtained are almost certainly a gross underestimate, for many siblings who were said to speak perfectly normally were in fact later observed in the clinic to have quite marked speech defects.

It was possible to obtain fairly full family histories in 75 of the 80 patients. The information in 5 of the illegitimate patients was too inadequate for analysis.

Speech defects.—In 18 cases one or both parents had a history of speech defect. The commonest defect was retardation of speech development, not apparently associated with abnormalities of hearing or mental

retardation. 10 mothers or fathers in 9 cases were noted not to have said their first intelligible words before the age of 2 years and to have noticeable articulatory abnormalities when they first went to school at the age of 5 years. 3 had been subjected to operation for "tongue tie" on account of their speech difficulties. In 7 cases one parent had a history of stammering or hesitation in speech during his or her school years, and in 4 the symptom was still apparent at the time of interview. In 2 cases the mother had "lisped" since childhood.

A history of one or more siblings suffering from speech defects was elicited in 24 cases. The defect was similar to that observed in the patient, specific developmental speech disorder, in 23 cases, and consisted of stammer in one. Specific developmental speech disorders affected only 1 sibling in 14 cases, 2 siblings in 5 cases, and 3 siblings in 2 cases. Thus 30 of the total of 131 siblings (approximately 23 per cent) were thought to show similar speech defects to those of the patients. The nature of the defect was confirmed by personal observation in 23. This figure takes no account of a number of very young brothers and sisters who had not yet developed speech and who might later show articulatory defects, and it is almost certainly an underestimate.

22 of the siblings were male and 8 female, giving a ratio of almost three to one. In 14 the developmental speech disorder had been, or was, severe enough to necessitate speech therapy, and 9 of them received treatment in the Hospital Clinic. The findings in brothers and sisters were often remarkably similar to those of the patients. It was often difficult to distinguish the tape recordings of the patient at a given age from those of a younger sibling made at an equivalent age or stage of speech development.

Handedness.—Accounts of handedness of parents and siblings were obtained from parents, but routine examinations of their handedness were not made. In 7 cases the mother or father was said to be left handed, and in 16 one or other ambidextrous. The prevalence of sinistrality amongst the 150 parents studied was 4·6 per cent and of ambidexterity 10·6 per cent.

Only the handedness of siblings over the age of 5 years was noted. 51 patients had 98 siblings over this age. In 5 cases 1 brother or sister was thought to be left handed, in 6, 1 brother or sister was considered to be ambidextrous, and in 3 cases 2 siblings were classified as ambidextrous. The prevalence of left handedness amongst those of school age was approximately 5 per cent and of ambidexterity 12 per cent, rather similar figures to those obtained for the parents.

History of Clinical Findings of the Patients

58 of the patients were boys, and 22 were girls, giving a male to female ratio of 2·64/1.

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The distribution of patients by birth rank was almost exactly what would have been expected in a random sample of children in these families. 43 of the 73 legitimately born patients were last born at the time of referral, but this is accounted for by the early age at which they were seen. Their parents had not had time to produce more offspring conveniently.

Birth histories.—15 of the 80 patients were known to have been born after pregnancy, labour or delivery which was definitely abnormal (Table II). In addition to these, 1 patient was born after the mother had

TABLE II.—ABNORMALITIES OF PARTURITION IN 80 PATIENTS WHO LATER SHOWED DEVELOPMENTAL SPEECH DISORDERS

	Child normal after delivery	*Child abnormal after delivery*
Abnormalities of pregnancy		
Pre-eclampsia	0	1
Ante-partum hæmorrhage or placenta prævia	3	0
Prematurity only	1	0
Abnormalities of labour and delivery		
Cord round neck	1	0
Cord round neck and prolonged labour	0	1
Prolonged labour	1	3
Breech delivery	1	1
Forceps delivery	2	0
	9	6
Abnormalities of the neonatal state		
Apnœa	0	5
Jaundice (1 Rhesus incompatibility)	0	4
Neonatal gastroenteritis	0	1
	0	10

had recurrent fainting spells during her pregnancy, 3 were born at an estimated forty-one weeks gestation, and in 2 with normal pregnancies Cæsarean Section was performed on account of the previous obstetric history. 11 patients were prematurely born by weight. The lowest birth weight was 3 lb. 10 oz.

A total of 16 patients showed transient abnormalities in the neonatal period. 6 of these were born after abnormal and 10 after apparently normal pregnancies, labours or deliveries. Neonatal apnœa lasting over one minute was the commonest abnormality of the neonatal period. It occurred in 6 cases, in 2 of whom it lasted for more than two minutes. 4 cases were jaundiced in the neonatal period. In 3 this was thought to be physiological, and in one due to erythroblastosis. A single exchange

transfusion was given in the latter case. None of the patients showed persistent abnormalities in the neonatal period, and none was considered to have been birth damaged at that time.

Motor milestones and general health.—The motor milestones of patients were not strikingly outwith normal limits. The great majority were sitting without support before the age of 8 months. 12 patients walked without support before the age of 12 months. 36 walked between the ages of 12 and 15 months, 23 between 15 and 18 months, and only 9 after the age of 18 months.

Apart from there being a rather high prevalence of respiratory infections in early life amongst the prematurely born children, the amount of illness amongst the patients was not striking.

6 patients had a history of recurrent respiratory infections or bronchitis after the age of 2 years. 16 patients had had recurrent tonsillitis. Single children had histories of respectively, eczema, asthma, knock-knee, pink disease, cervical abscess and congenital heart disease. 2 showed hypomandibulosis, and 6 abnormalities of dental occlusion, 2 were epileptic and both had a family history of recurrent convulsions. 3 children, 2 of whom were prematurely born, were noted to have convergent strabismus of non-paralytic type. None of the children in the series showed other significant neurological abnormalities.

Clinical findings.—At the time of examination 7 children had enlarged tonsils, 3 enlarged adenoids associated with post-nasal catarrh, and in 11 both tonsils and adenoids were enlarged. As has been noted, a further 6 had hypomandibulosis or abnormalities of dental occlusion (Table III).

TABLE III.—LOCAL ABNORMALITIES OF THE ARTICULATORY APPARATUS IN 80 PATIENTS WITH SPECIFIC DEVELOPMENTAL SPEECH DISORDERS

Abnormalities	*Associated with abnormal palatal movements*	*Associated with abnormal tongue movements*	*Associated with abnormal palatal and tongue movements*	*Not associated with any local interference*	*Total*
Enlarged tonsils only	1	0	1	5	7
Enlarged adenoids only	1	1	1	0	3
Enlarged tonsils and adenoids	1	2	1	7	11
Hypomandibulosis	0	2	0	0	2
Other malocclusion and dental abnormalities, e.g. open bite, diastasis of incisors	0	2	0	2	4
Tongue thrust only	0	1	0	0	1
Total	3	8	3	14	28

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In both cases of hypomandibulosis, 2 of the 4 cases of dental malocclusion, and 1 without other local abnormalities, involuntary protrusion of the tongue occurred during speech. In 14 of the 28 patients with local abnormalities there was interference with the movements of the articulatory organs. In the other 14 no interference could be demonstrated. Little knowledge of phonetics was required to eliminate the local abnormalities as the major cause of the articulatory difficulties in the patients. For example, whilst involuntary forward protrusion of the tongue might cause a number of sounds, especially sibilants, to be abnormal, it could not be held responsible for faults in such a wide variety of consonants as were found. In the majority of cases local abnormalities could be regarded as no more than contributory causes of the speech defects. No patients had a hearing loss of more than 15 decibels in both ears between sound frequencies of 500 to 6,000 on pure tone audiometry.

Laterality of patients.—The handedness, eyedness and footedness of patients was assessed by the rough clinical tests already described, and was compared with a series of 200 children between the ages of 4 and 7 years without speech defects or obvious neurological abnormalities admitted to the wards of the Royal Hospital for Sick Children (Table IV).

TABLE IV.—THE HANDEDNESS, EYEDNESS AND FOOTEDNESS OF 80 PATIENTS WITH SPECIFIC DEVELOPMENTAL SPEECH DISORDERS COMPARED TO 200 HOSPITAL PATIENTS WITHOUT SPEECH DEFECTS

	Percentages					
	Hand		*Foot*		*Eye*	
Laterality	*Patients*	*Others*	*Patients*	*Others*	*Patients*	*Others*
Right	46·25	78	60	76	62·5	75
Not strongly lateralized	50	14	27·5	10	8·75	4
Left	3·75	8	12·5	14	28·75	21

It was found that 37 of the 80 patients were right handed, three left handed, and 40, or exactly half, ambidextrous to a greater or lesser degree. 22 (27·5 per cent) showed little preference for one foot more than the other. The majority of patients were right eyed, though more were left eyed than were left footed or handed.

These results show that there is a significantly greater proportion of patients who show little preference for hand or foot amongst the patients as compared to the controls, X2 being 10·8 and 13·7 respectively. The proportion of patients showing little laterality of eyedness is not significantly different from the proportion in the 200 controls.

Speech development.—The ages at which the patients were reported to have said their first consistently intelligible words other than "Mama," "Dada" or equivalents, were late. In 54 cases intelligible words were only heard after the child was 18 months of age or more, in 25 after the age of 24 months, and in 17 after the age of 30 months. The development

of the ability to form phrases and sentences was also retarded, as indicated in Table V. In most cases the length of time it took children

TABLE V.—THE SPEECH DEVELOPMENT OF 80 CHILDREN SUFFERING FROM SPECIFIC DEVELOPMENTAL SPEECH DISORDERS
(All but 9 children walked before 18 months)

Speech development	*Total*	*With receptive difficulty*	*Without receptive difficulty*	*With language difficulty*	*Without language difficulty*
Words before 18 months and phrases before 30 months..	21	5	16	4	17
Words before 18 months and phrases after 30 months .. / Words after 18 months and phrases before 30 months..	10	4	6	7	3
Words after 18 months and phrases after 30 months ..	49*	21	28	29	20
Total	80	30	50	40	40

*Of these 49 children { words came after 24 months and phrases after 36 months } in 22 cases.
{ words came after 30 months and phrases after 42 months } in 15 cases.

with intelligible single words to join them together appeared to be approximately proportional to the age at which they had first said the single words. Thus patients who were only slightly retarded in the age at which they had first used intelligible single words would make intelligible phrases in a few months. In contrast, those whose first intelligible words had appeared only after the age of $2\frac{1}{2}$ years usually began to say phrases only after a year or more had elapsed.

The first words uttered by patients were usually intelligible only to the mother and other siblings, though occasionally domesticated fathers would also be able to understand them. Even when the stage of joining words together had been reached, what they said was usually unintelligible to adult strangers because of the omission, substitution and faulty articulation of consonants. The common descriptions by parents were that "The ends of the words were missing," "He jumbles up the sounds so one word might just as well be another," "He's never got over the stage of baby noises," "He imitates the baby all the time." In some cases parents noted that sounds which were correctly articulated at the beginnings of words were incorrectly spoken if they occurred in the middle or end portions. As the patient matured the parents usually noticed that the proportion of defective sounds decreased and speech consequently became more intelligible. In almost all cases it was found not too difficult to understand after the age of about 6 years.

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As well as having faults in pronunciation, many patients make gross errors in syntax. Parents complained that prepositions, conjunctions, auxiliary verbs and articles were often omitted. Less frequently the order of words was reversed or an appropriate word replaced by an inappropriate one which might sound rather similar. Like the faults of articulation, so the disorders of language tended to become less marked with maturity.

On examination all the children showed defective articulation of consonant sounds. Unacceptable articulation of vowels was uncommon. The most frequently defective consonants were those which were usually last to be acquired by normal children. Consonants which were normally acquired early, for example "m" and "n," were less frequently abnormal (Sheridan, 1945). The frequency with which the various consonants were found to be abnormal is indicated in Table VI.

TABLE VI.—MOST FREQUENTLY MISPRONOUNCED, SUBSTITUTED OR OMITTED SOUNDS IN 80 CHILDREN WITH SPECIFIC DEVELOPMENTAL SPEECH DISORDERS

Sounds	*Group* 1 *% with defective sounds*	*Group* 2 *% with defective sounds*
r	78	37
ʃ (sh)	74	15
θ (*th*ing)	66	31
s	63	5
l	62	1
k	36	12
tʃ (*ch*urch)	34	13
dʒ (he*dg*e)	34	13
g	26	9
f	20	6
v	17	—
p	17	1
b	17	—

Group 1.—80 children with specific developmental speech disorders.

Group 2.—Sample group of 112 unselected children aged $3\frac{1}{2}$ years (Morley, 1957).

The articulatory defects were often inconstant. For example, in many cases sounds were quite well articulated at the beginnings of words and sentences but faulty in their middles and ends. They were more often defective in words which had been recently acquired than in those which had been in the patient's vocabulary for a long time. Thus one child who still called his sister Kathleen, "Tateen" (one of his first words), said "I came in a black car" quite clearly. The habit of faulty articulation of well-known words tended to persist after the patient had learnt to pronounce their constituent sounds correctly.

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At a later stage of articulatory development consonants which the child had learnt to pronounce correctly when they occurred singly, were defective when reduplicated or in association with other recently acquired consonants. Thus a child with normal "s" and "t" sounds, who might even be able to articulate "st," would find it impossible to produce either of the "st"s in "wrist strap."

There was often a marked difference in the intelligibility of spontaneous and imitated speech. Some children could repeat nursery rhymes containing a number of late acquired consonants quite understandably line by line after an adult but be quite unintelligible when reciting without help. Speech was noticeably less intelligible when patients were tired or excited than when fresh and at ease.

The extent to which the intelligibility of speech was impaired varied in the different patients. In some with only a few late acquired consonants defective, the patients could express themselves without much difficulty. They were often diagnosed by speech therapists as suffering from "dyslalia." In severe cases, in which few if any consonants were consistently articulated correctly, speech was quite unintelligible, and speech therapists diagnosed them as suffering from "Idioglossia."

40 of the patients with developmental articulatory defects showed abnormalities of speech which are conveniently, if arbitrarily, classified as language disabilities. There was reversal or alteration in the order of syllables in long words, or syllables might be omitted or substituted by others which were inappropriate. Sometimes the last syllable of one word or phrase would be attached to the next, and less commonly appear half-way through the succeeding sentence. Neologisms which made speech quite unintelligible resulted. The substitution of words by others which were inappropriate, though they often sounded rather similar, further interfered with patients' intelligibility. Inversion and other disturbances of word order occurred quite commonly, especially when patients were excited.

The omission of small words, especially those with only syntactical significance, such as conjunctions, prepositions, auxiliary verbs and articles, was often striking. Even when it had disappeared from speech this trait sometimes persisted in reading and writing. The ends of sentences were sometimes lacking, and when excited, patients sometimes began three or four sentences in succession without proceeding far enough with any of them to convey their meaning.

Alteration of the rhythm of speech was not uncommon, but definite stammer was only observed consistently in 2 patients and hesitation in 1. A failure to develop normal patterns of intonation and stress was noted in the majority of patients with severe language difficulties. As a result their speech was often quite noticeably monotonous and had a curious impassive quality. Stress and intonation disorders require much

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experience in phonetics for their detailed analysis, however, and no consistent study was made of these in this series.

Comprehension difficulties.—A number of parents had suspected that their children might be deaf in earlier years, not merely because of their inability to speak but because they seemed to have difficulty in understanding what was said to them. This was more often noted in children with relatively severe retardation of articulatory development than in those who were mildly affected.

Often the patients had acquired the habit of saying "Eh?," "What?," "Beg pardon?" almost routinely whenever they were addressed. For their part, parents had often learnt to repeat everything they said to the child, often accompanying what they said with gestures. It was interesting, however, that very few of the parents who were interviewed ever confessed to gesturing themselves, though they had noticed their spouses doing so. As the patients matured, their comprehension of what was said to them improved, though their habit of "Eh"ing and "What"ing often persisted for years.

On examination a number of patients could be observed to watch attentively the faces of people talking to them, and they often seemed to respond to gestures more rapidly and easily than to what was said. A distinct momentary gap between the child hearing the voice and giving signs of comprehending what had been said was present in 30 patients. Parents' stories suggested that a further 12 patients had shown similar difficulties in comprehension in previous years who did not show them by the time they were examined. When one pointed out the "gap" to parents, they commonly said something like "Yes, he's always like that; it takes a moment for the penny to drop, but he's intelligent all right." Difficulties in comprehension of this type appeared to improve more rapidly than articulatory defects as the child matured. They were commoner in children with severe retardation of speech development than in those with relatively mild speech symptoms.

Psychological Examination

All 80 children in the series were given the Terman Merrill test and 28 the Wechsler Verbal and Performance Tests also. The results obtained were often difficult to interpret in view of the youth of many of the patients and the difficulties experienced by the testers in understanding what they said. The results of the Terman Merrill tests are shown in Table VII. It will be observed that only 2 of the children scored less than 80, and 7 (8·75 per cent) scored more than 120. The majority of the 32 patients to whom the Wechsler tests were presented scored better on the performance than the verbal scale, but the mean difference was only 9 points. The sub-tests which were most poorly done were "Comprehension" and "Vocabulary."

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TABLE VII.—INTELLIGENCE AND PSYCHIATRIC SYMPTOMS OF 80 PATIENTS WITH SPECIFIC DEVELOPMENTAL SPEECH DISORDERS

Intelligence	*Approximate I.Q. (Terman Merrill)*	*No.*	*Psychiatric symptoms (non-exclusive)*	*No.*
Superior	120+	7	Withdrawn and/or solitary	11
High average ..	110–119	16	Emotional, excitable ..	4
Average	90–109	42	Dependent, immature ..	7
Low average ..	80–89	13	Thumb-sucking	2
Dull and backward..	50–79	2	Temper tantrums ..	4
			Night terrors	1
			Enuresis	3
	Total	80	Total number with one or more of the above psychiatric symptoms ..	25
			No. under treatment at Dept. Psych. Med. ..	10

These results, whilst they can be recognized only as reasonably accurate, do indicate that the retardation of speech cannot be attributed in the majority of cases to mental retardation.

Educational difficulties.—Since the majority of patients were under the age of 5 at the time of referral, there has not yet been time to assess the prevalence of specific dyslexia and dysgraphia amongst them. Of the 15 patients over the age of 5 at the time of referral, 8 have given evidence of considerable difficulties in learning to read and write which cannot be attributed to inadequate intelligence. The errors made in reading and writing consisted of the omission of small words, reversal of word order, inversion and misplacement of syllables within large words, reversal of small words and letters, and difficulties in relating the spoken to the written symbol. They were identical to those described in patients with developmental aphasia in a previous paper (Ingram and Reid, 1956).

All the 7 patients with specific educational difficulties of this type had their first intelligible words only after the age of 24 months, and phrases after the age of 36 months. They showed moderately severe or severe articulatory defects for their ages at the time of examination. Their teachers had been indirectly responsible for referring 4 of them to the Speech Clinic.

Psychiatric disorders.—The psychiatric disorders encountered amongst patients are shown in Table VII. It will be observed that 25, or approximately 34 per cent, had one or more symptoms. Solitariness, manifest as inability to play with other children, day dreaming, lack of awareness of environment, introspection and poor concentration were the commonest. 7 patients were noted to be excessively dependent upon their mothers and immature in general behaviour. In spite of

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good intelligence in some cases they tended to play with younger children, resented being left alone and reacted to frustration or disappointment by temper tantrums or tears. In children with severe comprehension difficulties, some of whom appeared to be unable to analyse even sounds in their environment less complex than those of speech, unawareness of the environment was striking. They seemed "wrapped up in themselves," unable to make satisfactory mature relationships with other people or communicate with other children. In several cases their behaviour resembled quite closely that found in autistic children.

In almost all cases any increase in emotional stress appeared to produce an exacerbation of the articulatory abnormalities, often with associated regression in language functions. Unfortunately the situation in which patients with developmental speech disorders found themselves were all too often stressful. People outwith their immediate circle failed to understand them. Children of their own age laughed at their babyish speech and often teased them quite cruelly. At school teachers would all too often make extremely heavy handed attempts to correct their speech and thus emphasize their disabilities to the patients. In older children unrecognized specific dysgraphia and dyslexia increased their difficulties and contributed to the acute sense of inferiority which many of them showed. In these circumstances it is hardly surprising that 10 of the 25 patients with psychiatric disorders required treatment in the Department of Psychological Medicine.

Discussion

The defects of pronunciation shown by the patients in the present series appeared to be due primarily to the retarded development of articulation. Consonants were more frequently defective than vowels. Consonant sounds which are acquired late by normal children were more frequently defective than those which came early. Patients aged 5 years might make articulatory errors characteristic of normal 3- or 4-year-olds.

Speech defects of this type have been variously classified in the literature. When mild they have often been included in the confused mixed category of dyslalia. When they are severe enough to impair the intelligibility of speech they have been termed idioglossia (Guthrie, 1907; Worster-Drought and Allen, 1929; Seth and Guthrie, 1935; Brain, 1955).

Language Defects

It has long been realized that a proportion of patients suffering from severe retardation of articulatory development ("idioglossia") had associated retardation of language development and impaired ability to perceive the spoken word, termed variously "developmental aphasia," "congenital aphasia," "congenital auditory imperception," "congenital word deafness" (McCready, 1910, 1926; Allen, 1932; Morison, 1930).

These children show a characteristic reliance on gesture, facial expression and movement of the lips, rather than on the spoken word, and this has been well described by McCready (1926) and Allen (1932). In severe cases of "congenital auditory imperception" the discrimination of sounds much less specialized than those of speech is achieved very slowly, and deafness is often suspected in the first two or three years of life. The recognition of words and perception of their significance in speech is even more retarded and occasionally never achieved (Worster-Drought and Allen, 1929; Karlin, 1954).

In a recent study of speech disorders in childhood a distinction is made between patients with retarded development of articulation who have associated retardation of language development, and those without retardation of language development. They are classified respectively as suffering from "developmental aphasia" and "developmental articulatory apraxia" (Morley, 1957). The articulatory defects in these categories appear to be similar, and since it is admitted that the development of language may be slightly retarded in "developmental articulatory apraxia" it is difficult to see on what basis they are so clearly distinguished. The author herself admits that "developmental aphasia" and "developmental articulatory apraxia" commonly co-exist (Morley, 1958).

Educational Difficulties

Patients suffering from "congenital auditory imperception" may later show specific difficulties in reading and writing—"specific dyslexia" and "specific dysgraphia" (McCready, 1926; Worster-Drought and Allen, 1929). Conversely many children with specific reading and writing difficulties will be found to have had retarded speech development.

The reading and writing difficulties have been much studied (Fildes, 1921; Orton, 1937; Schilder, 1944; Schonell, 1948). They have been classified as follows: inability to perceive the relationships of shapes and letters in space and in reproducing these relationships correctly; failure to relate phonic and written symbols correctly to each other; difficulty in appreciating the meaning of the spoken word and the written word even when the latter has been correctly interpreted in phonetic terms (Ingram and Reid, 1956). Thus the educational difficulties are not due only to impaired abilities in the sphere of spoken language. There is frequently disturbed appreciation of spatial relationships, especially in the horizontal plane. This results in mistakes being made in recognizing the identity and order of letters and small words in reading and in letters being incorrectly formed (often reversed) and placed in incorrect relationship with one another. These spatial difficulties may be regarded as part of a general lack of appreciation of orientation in space (Bender, 1952).

Patients in the present series have not been observed for long enough

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for it to be determined whether dyslexia and dysgraphia are confined to those with retarded language development or not. It will be of great interest to compare in a few years' time the prevalence of specific dyslexia and dysgraphia in those with and without retardation of language development.

The Significance of Developmental Articulatory Defects

The articulatory defects described in the present series cannot be attributed to local abnormalities of the articulatory organs or to interference with their function as a result of local disease. They were not associated with significant mental retardation in the majority of patients and hearing was not significantly depressed in any of the cases described. Explanations of the articulatory defects must be sought in disturbances of the processes normally involved in the acquisition of speech, rather than by attributing them to active disease. Unfortunately there are few detailed studies of the development of language and articulation based on large series of children. Well-defined standards with which to compare obviously abnormal speech and articulation at different ages are lacking.

Much of what has been written about developmental aphasia, dyslexia and dysgraphia is based on studies of the disintegration of spoken and written language functions observed in adult aphasics. Much of this work on acquired aphasia and related disorders can hardly be applied usefully to children in whom language functions are developing and who show no other evidence of brain disease.

It may be that "developmental articulatory defects" may be regarded as manifestations of a "lower level" type of aphasic disorder than that which results in language abnormalities. As in acquired aphasia of adults it is probably misleading to emphasize the distinction between language and articulatory disorders too strongly (Critchley, 1952). Certainly the placing in separate major categories of patients with similar articulatory defects who have and have not language disturbances seems unrealistic. While it is true that "receptive difficulties" may be recognized in the former group of "developmental aphasia," and not in the latter group of "developmental apraxia" it is quite likely that in both groups of patients there are much more complex and "central" disturbances of language function.

To a limited extent only, it is possible to interpret the clinical manifestations of patients in the series in terms of severity of a postulated "developmental speech disorder syndrome." Thus patients with mild developmental disorders of articulation less commonly had retardation of language development and obvious language disorders than those with severe articulatory abnormalities. The retardation of language development was approximately proportional to the severity of the articulatory

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disorders. Patients with marked language disorders and comprehension difficulties showed more severe retardation of speech development than those without (Table V).

In these terms slight developmental articulatory defects only may be regarded as a mild manifestation of "the developmental speech disorder syndrome." More marked articulatory defects of the same type associated with retardation of language development may be classified as a more severe version of the syndrome. A severe form of "the developmental speech disorder syndrome" would consist of major developmental articulatory defects with great retardation of language development associated with defects of comprehension. The most severe manifestations comprise gross comprehension difficulties with poor appreciation even of less complex sounds than those of speech and only very rudimentary speech development. Patients with these clinical features have been well described by Worster-Drought and Allen (1929) and Karlin (1951) as suffering from severe "auditory imperception."

It seems likely that specific dyslexia and dysgraphia occur more commonly in children with retarded language development than those without. But many patients with educational difficulties show poor ability to perceive the significance of letter and word shapes and their orientation in space, as well as difficulties in the perception, comprehension and utterance of spoken speech sounds. More research is necessary before it is possible to relate the severity of these "spatial difficulties" to the severity of articulatory and language disorders.

Laterality

There has been much discussion in the literature about the apparent association of "mixed laterality," "cross handedness and eyedness," "changed sinistrality" with developmental articulatory disorders, developmental aphasia, stammering and specific dyslexia and dysgraphia (Orton, 1937; Macmeeken, 1939; Brain, 1945; Hallgren, 1950; Granjon-Galifret and Ajuriaguerra, 1951). It was suggested in a previous paper that weak laterality of handedness, eyedness and footedness, most often manifest as persistent ambidexterity was a more constant and important association than "crossed handedness and eyedness" and than left handedness, whether "converted" or left in peace (Ingram and Reid, 1956). In the present series it was interesting to observe that the proportions of patients with little lateralization of handedness, eyedness or footedness were similar whether there were language difficulties or not and whether there was impaired ability to comprehend speech or not.

It has been suggested that lack of laterality, due to failure of the development of hemisphere dominance, may be associated with agenesis of the nervous centres or tracts concerned with speech (Brain, 1945; McCready 1926).

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Ætiology

It is widely accepted that "congenital auditory imperception," "developmental aphasia" and specific developmental dyslexia and dysgraphia occur in children who show no clinical evidence suggesting cerebral damage and who are commonly of average intelligence (Hallgren, 1950; Karlin, 1954). Specific dyslexia, which occurred in 10 per cent of the unselected children reviewed by Hallgren, and specific dysgraphia are commoner than developmental aphasia or congenital auditory imperception (Karlin, 1954). Males are more commonly significantly affected than females in all these disorders (McCready, 1926; Hallgren, 1950).

A family history of retarded language development was reported in one-third of all patients with congenital auditory imperception by McCready (1926). Hallgren found sufficient evidence to suggest that specific dyslexia was inherited as a Mendelian dominant trait with partial penetrance of the gene. A history of speech defects in the family is commonly found in patients with "developmental aphasia" (Morley, 1957). In the present series full details of speech and educational difficulties in other members of the family were not obtained, but a high proportion of patients had parents and siblings with developmental speech disorders. The proportions of patients with a positive family history were similar whether there was retardation of language development and language disorders or not.

It seems legitimate to conclude that retardation of articulatory development often associated with language disorders may be familial, and genetically determined. The cerebral abnormalities caused by the gene are unknown. Brain (1945) suggests that there is incomplete development of the tracts in the brain concerned with speech and that this is associated with a failure to acquire normal hemisphere dominance. Suggestions that the gene is expressed as a "local aphasia affecting those parts of the brain concerned with the reception and association of sounds" lack neuropathological proof (Worster-Drought and Allen, 1929).

Summary

The histories, speech defects and clinical findings of 80 children with retarded development of articulation have been presented. 58 were boys and 22 were girls. 55 were under the age of 5 years.

It was found that a high proportion of patients had a family history of similar speech defects.

High proportions of patients had retarded speech development, language disabilities and impairment of their ability to comprehend what was said to them. A higher proportion showed little lateralization of handedness and footedness than a control series. Older patients frequently showed developmental dyslexia and dysgraphia.

The articulatory defects could not be attributed to mental impairment, hearing loss or local abnormalities of the articulatory organs. They may be regarded as one of the manifestations of "the developmental speech disorder syndrome." The other manifestations include retardation of speech development, language disorders, comprehension difficulties and specific dyslexia and dysgraphia.

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PATHWAY FOR THE JAW-JERK IN MAN

BY

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THE stretch or myotatic reflex of mammalian striated muscle (Liddell and Sherrington, 1924) is subserved by an arc of two neurones (Lloyd, 1943). The afferent nerve fibres take origin in muscle spindles (McIntyre, 1951; Hunt, 1952) and enter the spinal cord in the usual manner by way of posterior nerve roots; collaterals from these fibres (Cajal, 1952) make direct synaptic contact with motor neurones supplying the muscle within which the spindle receptors lie, and with those of its synergists (Lloyd, 1946). Integrity of the stretch reflex arc is tested by the clinician when he elicits a tendon reflex. The jaw-jerk is a stretch reflex, but the anatomical arrangement of the myotatic reflex pathway for the jaw-closing muscles appears to be different from the pattern found in the spinal cord. Experiments in the cat have shown that both afferent and efferent limbs of the reflex arc run in the motor root of the trigeminal nerve, the cell-bodies of the afferent neurones being large unipolar cells of the mesencephalic nucleus (Cajal, 1952; Corbin, 1940; Szentágothai, 1948; McIntyre, 1951). The work reported in this paper indicates that a similar arrangement occurs in man, the jaw-jerk having been found to persist after complete division of the sensory root fibres.

METHODS

4 patients were investigated who had had trigeminal sensory root division on one side for trigeminal neuralgia (*tic douloureux*). In three the section was subtotal with some remaining sensation in the ophthalmic division and in one the division was complete. One normal subject was studied also. The jaw-jerk was elicited in the usual way, and the reflex response monitored by oscillographically displaying and photographing the amplified action potentials of the masseter muscles led off by way of concentric needle electrodes (Adrian and Bronk, 1929) from about the mid-point of each muscle. A standard dual-channel electrophysiological recording outfit was employed, permitting simultaneous display of the action potentials from both masseter muscles. As in the technique described by Malcolm (1951), the oscilloscope sweep was triggered by impact of the head of the percussion hammer which contained a microswitch. If no response was elicited by jaw percussion,

reinforcement by clenching of the fists was practised. Configuration of the jaw-jerk action potential patterns was fairly constant for any given electrode position, but their form was readily altered by moving the needle tip. Latency of reflex response was measured from the start of the sweep to the first deflection of the reflex action potentials.

RESULTS

The jaw-jerk could be repeatedly elicited in two of the four patients, and in another, a stretch reflex response appeared inconstantly in a small proportion of repeated trials. No reflex response of either masseter muscle could be elicited, even with reinforcement, in the remaining case. The jaw-jerk was readily obtained in the normal subject. In each of the patients with a positive jaw-jerk, action potentials appeared in the masseter muscle of the operated side at a latency similar to that of a normal response. Fig. 1 presents records which illustrate this finding

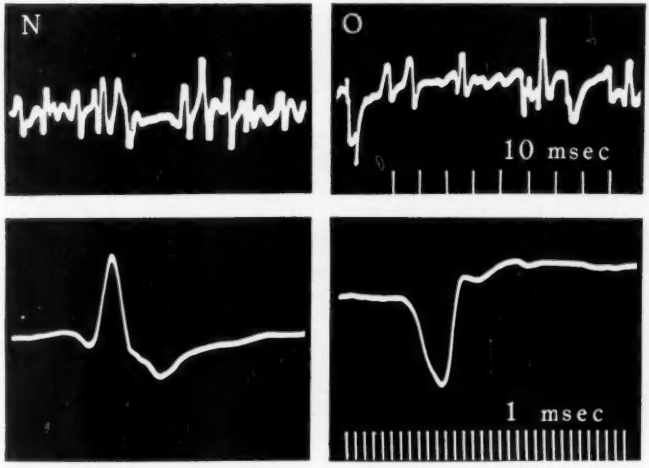

FIG. 1.—Action potentials of right (N) and left (O) masseter muscles in a patient who had had complete division of the sensory root of the left trigeminal nerve ten days previously. Upper records, potentials during voluntary clenching of the teeth, photographed at slow sweep (shown by 10 msec. time marks). Lower records, action potentials elicited on each side by tapping the mental protuberance, the start of the sweep signalling impact of the percussion hammer. 1 msec. time marks apply to these lower records.

and is taken from the patient with complete trigeminal sensory root section. The tracings on the left, labelled N, are from the normal side, and those on the right, designated O, are from the operated side in the same patient. The upper records, at slow sweep speed, show the action potentials of the two masseter muscles upon voluntarily clenching the

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jaw. The two lower records, at faster speed, show the action potentials of the jaw-jerk in the same muscles; it can be seen that the reflex latencies are approximately the same on the normal and operated sides. In this patient, the average latency on the normal side was 7·4 msec., and on the operated side 7·2 msec.; the spread of individual measurements was approximately the same for the two sides, with extremes of 6·1 and 8·2 msec. Latencies of this order were found in the other two patients with positive jaw-jerks and in the normal subject, the average reflex latency for the pooled results being 7·4 msec., with extremes of 5·8 and 10·1 msec. for the whole series of measurements.

It is possible from our results to make an estimate of the synaptic delay for the jaw-jerk. When a reflex is elicited by "natural" stimulation of receptors as in the present experiments, considerable variation in the overall latency is to be expected, for the afferent input is not a truly synchronous volley, but a relatively prolonged barrage which must vary in intensity and suddenness of onset from trial to trial. This inconstancy of afferent input, together with the inevitable excitability-fluctuations at synaptic junctions, account for the variation in reflex latency actually observed. Obviously, the responses of shortest latency provide the best gauge for estimation of the minimum pathway for the reflex. The shortest latency observed (approximately 6·0 msec.) represents the sum of the following time delays: delay in initiation of the afferent volley; afferent conduction time; central delay; efferent conduction time; intramuscular delay due to neuromuscular transmission and conduction of the muscle impulse.

Receptor delay.—Delay in onset of the afferent discharge is the most difficult of these factors to assess in the absence of actual records of the discharge. Elasticity of the tissue will delay the application of stretch to the spindle receptor terminals themselves, and there will be a further receptor latency before actual firing begins. We consider that about 1·0 msec. should be allowed for the time delay between impact of the percussion hammer (signalled by the start of the sweep) and onset of the burst of afferent discharge.

Peripheral nerve conduction.—On the assumption of equal conduction velocity in the afferent and efferent limbs of the reflex arc, peripheral conduction time can be assessed from the total length of the pathway (twice the distance between the mid-point of the masseter muscle and the trigeminal motor nucleus) and from the diameter of the largest fibres in the motor root. The conduction distance, as measured in the cadaver, is from 20 to 25 cm.; the diameter of the largest fibres in a fresh post-mortem specimen of a human trigeminal motor root stained with osmic acid was about 17 μ. Fibres of this size should conduct at approximately 100 metres/sec. at 37° C. (Hursh, 1939), so that peripheral conduction of impulses accounts for 2·0 to 2·5 msec.

Intramuscular delay.—On the basis of experiments with leg muscles, neuromuscular transmission and muscle conduction can reasonably be regarded as accounting for another 2·0 msec. Subtracting the sum of these estimated delays, 5·0 to 5·5 msec. in all, from the overall reflex latency of 6·0 msec., we are left the brief period of 0·5 to 1·0 msec. for central synaptic delay, which is too short to allow for more than one synapse. Thus a jaw-jerk taking place after minimal delay (presumably under the most favourable conditions for reflex transmission) appears to be mediated by a reflex arc of only two neurones, that is, it is a monosynaptic path as in the cat. It seems likely that the responses of longer latency are also mediated monosynaptically, but require in varying degree temporal summation of the synaptic action of repetitively-firing spindle afferents before discharge of motor neurones can occur. However, the existence of more complex, polysynaptic stretch reflex paths in addition to the monosynaptic route cannot be ruled out.

Discussion

Persistence of the masseteric stretch-reflex response after ipsilateral sensory rhizotomy of the trigeminal nerve shows that the afferent fibres subserving it do not enter the brain-stem by way of the ipsilateral sensory root, or at least that a substantial fraction of them must enter by some other channel. In all probability, this other path is the motor root as in the cat; however, the possibility must be considered that the jaw-jerk persists on the operated side because in these patients stretch is necessarily applied bilaterally, and one trigeminal nerve is intact. It is probable that some collaterals of spindle afferent fibres from the jaw-closing muscles cross the mid-line to reach motor neurones of their synergic contralateral fellows, but their action is likely to be limited to facilitation, and to be incapable of eliciting actual motor neurone discharge. In the cat, Sherrington (1917) noted the predominantly unilateral nature of the jaw reflex responses and Corbin and Harrison (1940) found that the mesencephalic root potentials came solely from the ipsilateral masseter muscle. It seems most likely that in man the pattern is the same as in the cat, the afferent fibres for the jaw-jerk entering the brain-stem by way of the motor root, and the cell bodies of the afferent neurones being large unipolar cells situated in the mesencephalic nucleus.

The peculiar arrangement of the stretch reflex pathway for the jaw muscles is of some general interest. Cajal (1952) drew attention to the unique, large unipolar cells of the mesencephalic nucleus, and in an admirable diagram not only showed axons of these cells running into the motor root, but also depicted collaterals from them entering the trigeminal motor nucleus. He had, in point of fact, defined the pathway for the stretch reflex of the jaw muscles, just as he correctly described the direct reflexo-motor collaterals in the spinal cord which subserve

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the stretch reflex for most of the skeletal musculature. However, at that time he could not, of course, appreciate the functional significance of these neural connexions. Weinberg (1928), in reviewing the problem of the trigeminal nerve and its connexions, put forward on morphological grounds the view that afferent fibres entered the brain-stem by way of the motor root to reach the mesencephalic nucleus, and that these fibres were probably proprioceptive in function. He was not able to throw light on their peripheral course and manner of termination.

Although Corbin (1940) took the matter further by showing degeneration of fibres in the mandibular branch after destructive lesions of the mesencephalic nucleus, it was not until the work of Szentágothai (1948) that Cajal's findings were fully confirmed and extended to the point of identifying the receptors from which the peripheral fibres of the unipolar mesencephalic neurones take origin. Szentágothai demonstrated in the cat that lesions of the mesencephalic nucleus caused degeneration of the receptor ramifications in muscle spindles of the masseter and temporal muscles, while the ordinary motor end-plates and Golgi tendon organs remained intact. Furthermore, he found degeneration of endings upon motor neurones of the trigeminal motor nucleus after such lesions in confirmation of Cajal's picture of direct collaterals to motor neurones from axons of the unipolar mesencephalic neurones. Corbin and Harrison (1940) were able to record action potentials in the mesencephalic nucleus upon stretching the ipsilateral jaw-closing muscles and as a result of pressure applied to the ipsilateral canine teeth or anterior part of the hard palate. Functional confirmation of Szentágothai's work was obtained by McIntyre (1951), who showed, also in the cat, an abundance of afferent discharge characteristic of muscle spindles in fibres of the peripheral end of the cut motor root upon stretching the masseter muscle, and that the stretch reflex was still present in this muscle after cutting the sensory root of the trigeminal, the motor-root remaining intact.

These various investigations together show that in the cat, the motor root of the trigeminal nerve carries the afferent fibres for the jaw-jerk, and that this reflex is monosynaptic as in the case of stretch reflexes in other skeletal muscles. The present work indicates that the same arrangement holds in man, a conclusion which provides an explanation for the preservation of masticatory function when the sensory root of the trigeminal is cut either singly or bilaterally for the relief of trigeminal neuralgia. Frazier introduced the refinement of sensory rhizotomy for the surgical treatment of this condition, his operation sparing the motor root and the ophthalmic sensory fibres (Spiller and Frazier, 1901; Frazier, 1921; Frazier, 1925). One of his patients retained satisfactory masticatory function despite division of the sensory roots on both sides and interruption of one motor root (Frazier, 1926). Recently, others have

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confirmed the feasibility of dividing both sensory roots in bilateral trigeminal neuralgia with preservation of masticatory function (Stookey, 1955; Wertheimer and Descotes, 1957). If the sensory root were the only channel of entry for trigeminal afferent fibres, this would be a surprising finding, in view of the devastating disintegration of motor function brought on by extensive posterior spinal root section in animals (Bernard, 1858; Mott and Sherrington, 1895). Frazier (1910) and Foerster (1913) both observed difficulty in control of voluntary movement after extensive posterior rhizotomy of the spinal cord in man. However, the presence of abundant proprioceptive afferent channels in the intact motor root provides a ready explanation for the preservation of co-ordinated masticatory function after interruption of the sensory root fibres pertaining to the maxillary and mandibular branches of the trigeminal nerve.

Summary

(1) Persistence in man of the jaw-jerk after operative division of the sensory root of the trigeminal nerve has been demonstrated in the masseter muscle of the affected side.

(2) It is concluded that the afferent fibres for the jaw-jerk in man enter the brain-stem by way of the motor root, as in the cat. The reflex pathway appears to be monosynaptic.

(3) The view is advanced that the unique arrangement of the stretch-reflex pathway for the jaw muscles explains the preservation of co-ordinated masticatory function after surgical division of trigeminal sensory root fibres.

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NOTICES OF RECENT PUBLICATIONS

THE RETICULAR FORMATION

Henry Ford Hospital International Symposium. Reticular Formation of the Brain. Editors, HERBERT H. JASPER, Montreal Neurological Institute, LORNE D. PROCTOR, Division of Neurology and Psychiatry, Henry Ford Hospital, ROBERT S. KNIGHTON, Division of Neurosurgery, Henry Ford Hospital, WILLIAM C. NOSHAY, Section of Neurology, Henry Ford Hospital, RUSSELL T. COSTELLO, Department of Medicine (Neurology) Wayne State University. Pp. 758. London: J. & A. Churchill, Ltd. Price 115s. net.

This book owes much to Dr. Magoun. His was the pioneer work which put the central reticular formation on the neurological map, and he was a participant in the Henry Ford Hospital International Symposium, in whose discussions his influence is very evident. The symposium, its editors state, could be considered a sequel to the symposium on "Brain Mechanisms and Consciousness" held in Quebec in 1953. It is perhaps indicative of the progress which has been made since then that the present symposium is much more factual and much less speculative. It consists of 36 contributions and the final summary. It covers the physiology of all known aspects of the central reticular formation by means of essays written by workers whose researches in this field are well known. It discusses the influence of the reticular formation on attention, perceptual discrimination and learning. It describes its relation with the endocrine system and the hypothalamus, its humoral effects and its pharmacology. It considers its relations with the cerebral cortex and its descending influences, and its conditioned reactions. It reports recent work on self-stimulation in animals. The discussion is brought to an end by a characteristic contribution on "The Reticular Formation and Clinical Neurology" by Sir Geoffrey Jefferson. Those who seek a comprehensive and authoritative review of this subject will find it here.

RUSSELL BRAIN.

The Waking Brain. By H. W. MAGOUN, Ph.D., Professor of Anatomy, University of California, Los Angeles. Pp. 138. Springfield: C. C. Thomas. Price 36s.

The Los Angeles School of Neurology led by Professor Magoun has been making notable advances in knowledge of the mechanisms in the brain-stem serving the states of sleeping and wakefulness. The brain-stem activating mechanism, of which little was known some ten years ago, is an ill-defined set of fibre-connexions which spreads from the medulla up into the mid-brain and from thence has connexions with the hippocampal region of the cerebral hemispheres. Through this part of the brain there are connexions to all areas, and there is a reverse flow too from cortex down to the brain-stem. The state of consciousness or alertness in which we live our active lives depends for its maintenance upon this mechanism, and very small lesions of it in the brain-stem produces a state in man and in animals which resembles sleep.

The importance of the discoveries which have been made in this fascinating field are twofold; first that there is no evidence that the cerebral hemispheres themselves are

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responsible for maintaining the state of consciousness, but that this depends upon phylogenetically much more lowly structures in the primitive brain, and second that consciousness is a state of alertness man shares with lowly animals but in which he uses his neopallium to differentiate himself from them by his activities.

In this short and lucidly written review Professor Magoun presents his evidence to those who are not specialists in this field, but who wish to keep abreast with an advance in knowledge which in its implications affects us all, but in its detail is bewildering.

DENIS WILLIAMS.

DISSEMINATED SCLEROSIS

Die Neuroallergischen Beziehungen in der Histopathologie der Multiplen Sklerose. By Dr. TIBOR LEHOCZKY, Akademiani Kiado, Budapest. 1957. Pp. 176. Berlin: Akademie-Verlag. Price 110 p.

This is an account of 20 cases of multiple sclerosis which have been investigated histologically in a most thorough way. The author's aim is to demonstrate, so far as is possible on the evidence of histology, the part played by allergy in this disease.

He is impressed with the frequency with which one finds œdema around developing plaques, together with swelling of the endothelium of blood vessels, and hyaline degeneration of the vessel walls, and he notes that such changes may be found at a distance from the plaques in what is apparently intact white matter. He describes not only perifocal œdema but also a distant moth-eaten ("Mottenfrass") appearance due, he believes, to general œdema. These and other perivascular forms of "Nervengewebs rarefikation" are interpreted as manifestations of neuroallergy. In 12 cases he has found the small granulomas described by Ferraro in multiple sclerosis and also by Goddard in experimental demyelination. Fresh hæmorrhages were noted in 5 cases, and old hæmorrhages in 3, but they were very scanty: he believes that they are part of the general allergic mechanism. In only 3 of the cases, however, did he find any evidence of thrombosis and this he regards as being against the theory of the thrombotic origin of plaques. In 2 cases there were no lesions in the cord but the brain was involved in each of the 20. The author believes that multiple sclerosis constitutes a continuing active dynamic process for in the oldest case he was able to find fresh foci of disease. He suggests that the mechanism is wrought either through a myelin-splitting enzyme or an antigen which has the specific property of destroying myelin.

Dr. Lehoczky has set out to substantiate what is now a popular theory of the mechanism of multiple sclerosis. One could criticize his selection of illustrations as being biased in favour of this viewpoint but not his very fair marshalling of the histological facts. He is to be congratulated on having adduced so much by means of the classical approach.

W. H. MCMENEMEY.

THE MENTALLY RETARDED

The Mentally Retarded in Society. By STANLEY POWELL DAVIES. 1959. Pp. 248. London: Oxford University Press. Price 45s.

This is a straightforward and objective account of the trends, apparent over the last fifty years, in caring for mentally handicapped persons in the United States. There, as here, the mentally defective person was one who was regarded with suspicious awe by a completely uncomprehending world until the concept of "mental age" became well understood as the result of applying carefully standardized tests. The author refers to Goddard's work in introducing the then new Binet-Simon

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test into U.S.A. He gives a good picture of the wave of alarm which spread over the country as computations were made of the vast numbers of mentally retarded persons, of their fecundity and their invariable presence at the root of social problem behaviour.

The extent of the State laws permitting sterilization illustrates the way in which panic legislation was brought in, but of course not invariably implemented. The prevailing opinion changed somewhat after the 1914–1918 war, and greater attention was given to segregation and training. But for a long time the emphasis lay in segregation, and it took pioneers such as Fernald and Goddard to focus interest in both the scientific and the humane approach to this problem.

More recently the emphasis has swung against the more extreme degrees of segregation towards the idea of the colony, with its working, largely self-supporting, population, and further on to the retention of the mentally retarded in the community, providing training and the opportunity of suitably safeguarded work to enable him to become at least partially self-supporting.

The chapter on changing concepts of causation deals with the question of heredity, without breaking new ground, and with less emphasis than might have been wished on newer concepts of morbid anatomy. The problems associated with cerebral palsy are no more than mentioned. However, this is not a medical textbook so much as a sociological survey and it summarizes admirably what is done for mentally retarded adults and children in U.S.A. The type and the format make the book a delight to handle and to read; perhaps this explains the relatively high price.

E. M. CREAK.

EPILEPSY

Temporal Lobe Epilepsy. Ed. MAITLAND BALDWIN, M.D., and PEARCE BAILEY, M.D. Pp. 581. Oxford: Blackwell. Price £5 17s. 6d.

The temporal lobe epilepsies are getting a lot of attention now, because they are common and are enigmatic. As "psychomotor epilepsy" or "epileptic equivalents" they were neglected by investigators because they had not the precision or stereotypy of *petit mal* or *grand mal* and so did not at first appeal to the applied physiologist. On the other hand the elaborate disturbances of behaviour or feeling interest so many kinds of clinical observer. The temporal cortex is accessible to physiological study and to surgical exploration, facts fully appreciated by animal experimenters, notably Klüver. It was consequently inevitable that teams of specialists should relate psychological to physiological change in patients with structural disease of the temporal lobe.

A number of these specialists from Europe and the States met in the National Institute of Health in Bethesda in 1957, and this volume records their discussions. These are excellent papers by well-selected participants, and the volume is much more successful than most verbatim records of this sort. All of the little we know of the basis of "temporal lobe epilepsy" is here, but a mass of minutely observed facts must be critically distilled by the passage of time to be of practical value to the clinician.

DENIS WILLIAMS.

The Epileptic Seizure. Its Functional Morphology and Diagnostic Significance. By C. AJMONE-MARSAN and B. L. RALSTON. Pp. 251. Springfield, Ill.: Thomas. Price £2 5s.

The authors state that the major emphasis of this text "has been placed upon the totality of events occurring during the activation of an epileptogenic process by Metrazol (to the point of inducing a seizure)." Although they acknowledge "that

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there is a large number of valuable diagnostic and patho-physiological data which remains to be utilized," they nevertheless hope that the publication of their observations "will help in the interpretation of spontaneous seizures." The observations summarize the clinical and EEG features of 153 seizures induced by the slow intravenous injection of Metrazol in 119 patients with epilepsy, and the observation of an attack induced in this way has become part of the routine investigation of such cases in their clinic as in many others. This procedure does not set out to be a therapeutic test on which to base a diagnosis of epilepsy, neither are the electrical changes of great localizing value: the primary purpose is to observe patients' attacks under favourable conditions so as to discover further relevant clinical details such as the transient aphasia, hemiparesis and hemianopia, which, experience shows, are liable to be missed by ordinary questioning of an epileptic and his relatives.

The book can be recommended for its review of the literature and for a good deal of incidental new information of an observational nature. Against this some would feel that the unrestrained use of percentages and proportions is unfortunate as it obscures the actual data. For example, when we read under the heading of Parieto-occipital Seizures that "two-thirds of cases had a mild hemiparesis" (p. 25), we have to bear in mind a table seven pages back which makes clear that in the particular group to which this statement relates there were only three cases. There is also a conspicuous absence of supporting pathological data in view of the fact that there are many statements apparently relating to localization of pathology. Nevertheless this is a useful introduction to an additional technique of investigation which may further our knowledge of the localizing value of certain features of the epileptic seizure.

J. A. V. BATES.

ELECTRONIC APPARATUS

Electronic Apparatus for Biological Research. By P. E. K. DONALDSON. Pp. 718. London: Butterworth. Price £6.

The book sets out in 700 pages a great deal of the experience of the Cambridge School of Physiology in electronic problems and one feels sure that it will find its way to most electrophysiological departments for there is no work of reference which contains so much practical information. Since it is sincerely hoped that the support it receives will mean that further editions are called for, the following comments are offered for the editor's consideration. Aside from minor errors which are notably few, any book of this type could be criticized on three grounds—the arrangement of the material, the omission of relevant information, and the textual clarity. There is no criticism with respect to the last point. The text is everywhere most readable—but is it a readable jumble? The book is divided into four sections headed respectively: Theory (282 pp.); Practice (50 pp.); Transducers Electrodes and Indicators (252 pp.); and Complete Apparatus (126 pp.). These titles themselves suggest that the difficult problem of arrangement of material may not have been overcome. The subject index is definitely inadequate by modern standards. There is no author index and this is a particular shortcoming in a field where one is apt to associate techniques with proper names, and there must be in all several hundred references quoted. Intra-text references would have helped the reader but they are almost absent. There are no appendices, where detailed practical information could have been collected together (wire gauge and coil-winding data, workshop equipment, etc.). In the first section (Theory), there are numerous practical tips scattered among the algebra. For example here we find practical suggestions on how to overcome instability in amplifiers (p. 160), and the only index reference discovered is under the entry "motor-boating." In a later edition perhaps this

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whole section could be pruned of material irrelevant to the title. The second section (Practice) seems unduly short, and to deal with the practical problems of valve selection in only 350 words and one table seems inadequate in a work of this type. Some of the practical problems not mentioned are heater-cathode voltage limits, and the effect of mounting position, dissipation and age on characteristics of some types. The section on "Faults" peters out after only 2,000 words when the author brings "this somewhat depressing chapter" to an abrupt close with a brief anecdote which revolves round an incompetent technician. In fact there is a very great deal to say about fault finding, and many most competent technicians may spend a long time at it baffled by the effects of resistors which become non-ohmic, parasites in power packs, not to mention the innumerable causes of interference at mains frequency. The chapter on stimulators concentrates on the generation of different waveforms, to the neglect of the problem of output impedance—that of some of the circuits given being too high for those types of bipolar stimulation where the inter-electrode resistance may vary between 500 and 1,000 ohms. Also no mention was found of the desirability of using a balanced (non-polarizing) output or of monitoring the actual stimulating wave-form which is now a standard practice in many laboratories. Again in the section on valve oscillators (p. 208–216) there is no mention or indication of suitable component values and valve types, and much time might be wasted in arriving at these.

To incorporate these and other additions, space could surely be found in several places. For example about 25 half-pages in Ch. 28 are occupied by graphs copied from manufacturers' data sheets relating to particular components. In each case the information relevant to the text discussion could be put into a sentence, and no one should rely on these graphs in practical work for manufacturers' data are not fixed. There are also 32 photographs of individual components (knobs, wire, etc.) which add very little indeed that is not known to any likely reader, and could be deleted.

But these criticisms are small when viewed against the great volume of useful information never before collected together and so clearly expressed, and all concerned are to be thanked in advance for the help their publication will be to all workers in the field of electrophysiology.

J. A. V. BATES.

BRAIN AND MIND

Brain. Memory, Learning. A Neurologist's View. By RITCHIE RUSSELL, *C.B.E.*, M.D., D.Sc., F.R.C.P. Lecturer in Neurology, University of Oxford. Pp. 138. Oxford: The Clarendon Press. Price 18s.

This is a delightful little book in which Dr. Russell has not tried to say too much in too few words At whatever length we write we cannot yet make much sense of what we know of the mechanisms of memory, or of the physical basis of consciousness or of pain, or of temperament, so no great harm can come from quiet and concise speculation of the sort found here. Besides, the clinical neurologist is fortunate, for he has entry into so many camps, and he claims the right to speak so many languages as well as his own—of the physiologist, psychologist, psychiatrist and even the philosopher—though he may not always be quite sure what all the words mean.

Dr. Russell is quite aware of all this, but he takes the reasonable view that someone must speculate, and he obviously enjoys doing so. He has the advantage of being an amateur in a number of his speculations, and so can escape the censure of the professionals, for whom he did not write this book. He has used his life-long interest in the effects of head injury and his close contact with the Oxford school of physiology to take his speculations a little way across the bridge between the brain and the min d

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Anyone who does that will be attacked by the experts at either end, but he may still achieve the gratitude of many onlookers, particularly if he presents his material and his deductions in an attractive way. Dr. Russell has, and doctors will enjoy a few quiet hours with him.

DENIS WILLIAMS.

POLYMYOSITIS

Polymyositis. By JOHN N. WALTON and RAYMOND D. ADAMS. 1958. Pp. 270. London: E. & S. Livingstone. Price 32s. 6d.

This is a detailed nosographical account of this fashionable syndrome, giving a clear picture of its clinical and pathological features, although it includes only a small series of personally observed cases. While the boundaries of this condition remain vague, terminology and classification may be matters of dispute. Following Eaton, the authors use "polymyositis" to refer to the clinical state as a whole and not to the pathological changes in affected muscle which, as they emphasize, are largely non-specific. They believe that "we are dealing in most cases with a single disease process related to the other 'collagen' diseases," and their clinical classification which largely stems from this tenet is logical and simple. They rightly stress the need for a careful search for underlying malignant disease, as well as the practical importance of distinguishing the more chronic forms of polymyositis from progressive muscular dystrophy. A valuable summary of the differential diagnosis between the two is included.

As this monograph also contains a comprehensive review of the relevant literature as well as an extensive bibliography, it can be recommended to those interested in the subject, though the conclusions reached upon the natural history, prognosis and value of steroids in treatment might have been more firm had they been drawn from a larger number of patients.

J. HAMILTON PATERSON.

THUDICHUM

Thudichum, Chemist of the Brain. By DAVID L. DRABKIN, Professor of Biochemistry, Graduate School of Medicine, University of Pennsylvania. Pp. 308. 52 illustrations. Published by Pennsylvania University Press. London: Oxford University Press. Price 40s.

Johann Ludwig Wilhelm Thudichum died in 1901: he remained forgotten for a quarter of a century. Even when Irvine H. Page in 1955 acclaimed him as the father of neurochemistry few had heard of him. Then came Professor McIlwain's appreciation of his work and now we have this biography. Thudichum, a graduate of Giessen and a pupil of Liebig, spent his professional life in London and a most productive one it was. Dr. Drabkin lists 213 items in his bibliography mostly on chemical topics, no mean achievement for a man who latterly had to earn his bread and butter as an otolaryngologist. Dr. (later Sir) John Simon recognized his worth and was ingenious enough to arrange for Thudichum's private laboratory to receive a government subsidy from 1864–1883. His first researches on the chemical constitution of the brain appeared as a supplement to the report of the medical officer to the Privy Council but his "Chemistry of the Brain" was not published until 1884. But Thudichum found time for many other pastimes; he was the father of a large family, he sketched, he refreshed himself with Beethoven quartets, he wrote on viticulture, œnology, plant pathology, and cookery, and served under Esmarch both in 1850 and in 1870. In 1864 he was the first recipient of the Sir Charles Hastings gold medal of the British Medical Association and also Lettsomian professor of the Medical

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Society of London. In 1885 he was elected president of the West London Medical-Chirurgical Society.

Dr. Drabkin provides a wealth of information about Thudichum but it is a discursive book and lacks sequence. Nevertheless, the reader cannot fail to share in the author's enthusiasm as he follows him in his quest for information and sees the jigsaw of this elusive man's life gradually pieced together: it is not only a biography but the odyssey of a devoted biographer. He is however at fault in saying that Sir Archibald Garrod was in his 92nd year in 1929 (p. 38 and fig. 8): he was in fact then aged 72. Appendix IV contains interesting correspondence with Esmarch, Liebig, Virchow, and Hoppe-Seyler. Appendix V is a charming tribute to the late Otto Rosenheim, to whose memory the book is dedicated.

W. H. McMENEMY.

SHORTER NOTICES

Psychiatry in Medical Practice. Ed. W. LINDESAY NEUSTATTER, M.D., M.R.C.P. London: Staples Press. Pp. 310. Price £2 2s. 0d.

Psychiatry in General Practice. By J. A. WEIJEL, M.D. Amsterdam and London: Elsevier Pub. Co. Pp. 208.

These are two very different works, the first a simple textbook for the family doctor, the second a plea for the recognition by the family doctor of his unique relation to his patient's psycho-social background. Dr. Neustatter has been helped by a number of his colleagues to produce a readable and popular book. Dr. Weijel who has based his textbook upon more academic scholarship has presented a stimulating monograph which will be appreciated by the professed psychiatrist.

Schizophrenia. By MANFRED SAKEL. 1958. Pp. xii+335. New York: Philosophical Library Inc. Price $5.00.

As the man who introduced insulin shock treatment for schizophrenia, the late Manfred Sakel showed himself possessed of gifts of the greatest value to medicine, such as intuitive imagination, enthusiasm, persistence and courage. His mental equipment, unfortunately, did not include clarity and orderliness of mind or the gifts of exposition. It is not possible to point to any merit in the work under review; and even Professor Hoff, who writes a sympathetic Foreword on the achievements of the author, makes no claim on its behalf. No service to the memory of Sakel has been done by this publication.

Neurological and Psychological Deficits of Asphyxia Neonatorum, with consideration of use of primates for experimental investigations. Ed. WILLIAM F. WINDLE, Sc.D. Oxford: Blackwell. Pp. 336. Price 60s.

A conference on asphyxia neonatorum, brain damage, and impairment of learning was held in Puerto Rico in 1956, sponsored by a number of philanthropic organizations, and the National Institute of Neurological Diseases and Blindness. This volume contains 15 essays which were presented, with discussions and much other material. The participants, all from the States, are eminent in this field and their contributions are succinct. There is an inclusive bibliography, but the subject index, which is essential to this kind of collection, is inadequate with just a hundred headings,

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A Textbook of Neurology. By H. HOUSTON MERRITT, M.D., Professor of Neurology, Columbia University. 2nd Ed. Pp. 765. Henry Kimpton. Price £4 13s. 6d.

This excellent text has reached its second edition in four years. It has been thoroughly revised and it is critically documented with selected references at the foot of each chapter and subsection. With Dr. Merritt's well-known interest in the accurate recording of clinical neurology based on morbid anatomy this feature makes the book a useful work of first reference to the professional neurologist.

Psychopathic Personalities. By Professor KURT SCHNEIDER, formerly Director, Psychiatric and Neurological Clinic, Heidelburg. Trans. by M. W. Hamilton, B.A., Tutor for Psychiatric Social Work, University of Manchester. Pp. 163. London: Cassell. Price 18s.

This German classic is now available in an excellent translation, most pleasant to read. It is particularly opportune that it should appear at a time when its title is so widely and uncritically used. Although Professor Schneider's nosological divisions of personality types in his last chapter may seem artificial, his lucid presentation of fact and opinion forms a most reasonable basis for discussion among psychiatrists of widely differing views.

Introduzione Alla Elettroencefalografia Clinica. By G. M. CORSINO. Pp. 195. Cappelli Editore. 1957. No price given.

This is a very useful text, thoughtful, practical, and well balanced. It is profusely illustrated from the extensive material in Dr. Corsino's laboratory. This fact, and its accurate documentation, makes it easy to follow the Italian text. American and English references predominate in the bibliography.

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